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THROMBOSIS OF THE DURAL SINUSES

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THROMBOSES of the dural sinuses give certain symptoms and signs dependent on the sinuses involved and the structures drained; these typical signs, however, may be modified by three separate conditions: first, the numerous collateral communications between sinuses and sinuses, and sinuses and veins; second, the anatomic variations in the position of the sinuses, and, third, the variations in size in the lateral sinuses; occasionally, one sinus may even be absent. On the presence of such anatomic variations, Woodhall [1] based the reasons for false positive and negative phenomena.

Dural sinuses are sluggish venous channels first lying in the dural sheath and later becoming formed vessels. They collect blood from the brain and its coverings as they course centrad, finally to become the jugular vein; the sinuses connect one with the other and are given different names, dependent on their localization.

With any thrombosis, there may be increased intracranial tension with its typical signs; relaxation of sphincter control of cerebral type may also occur. There may be coma.

THE DURAL SINUSES

1. The superior sagittal (superior longitudinal) sinus is centrally, superiorly and superficially located, circling the brain; posteriorly, it becomes the occipital sinus at its juncture with the straight sinus. Frontal, precentral, postcentral and occipital veins empty into it, draining the superior and mesial portions of the hemispheres.[2] These veins also anastomose with the middle cerebral and sylvian veins, which, in turn, empty into the cavernous sinus. This sinus and its tributaries drain the periphery and a small area inside the periphery of the brain,

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1. Woodhall, B.: Variations of the Cranial Venous Sinuses in the Region of the Torcular Herophili, Arch. Surg. **33**:297 (Aug.) 1936.

2. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1946, pp. 177-179.

so that blockage of this sinus may affect the upper motor neuron area and produce irritative phenomena. The motor nerve fibers that control leg movements rise highest; therefore convulsive seizures, paralyses and other disorders may begin in the muscles of the leg and foot. If motor paralysis is present, there will be anesthesia in the same area. Emissary veins may be clogged and the scalp edematous.

2. The inferior sagittal (inferior longitudinal) sinus lies in the dependent portion of the falx and empties into the straight sinus. This sinus, with the superior sagittal, forms the occipital sinus. Veins which drain the corpus callosum and the lower portion of the middle surface of the hemispheres empty into the inferior sagittal sinus. As might be surmised, the symptoms of occlusion in this sinus may be similar to those of a thrombosis of the superior sagittal sinus, but are apt to be severer.

3. The straight sinus is a continuation of the inferior sagittal sinus and receives the superior cerebellar veins and the great vein of Galen (great cerebral vein). The latter drains the midportion of the hemispheres, including the central white matter, basal ganglions, ventricles and choroid plexus. The straight sinus empties at the junction of the superior sagittal and occipital sinuses. Since the basal nuclei are involved in thrombosis of the straight sinus, decerebrate rigidity may appear, with convulsions or fits of a spastic nature, and usually the patient is unconscious.

4. The transverse (lateral, sigmoid) sinuses begin at the junction of the superior sagittal, occipital and straight sinuses and pass laterally and anteriorly on each side in the border of the tentorium to the base of the petrous portion of the temporal bone. At this point they leave the tentorium and pass down into the jugular bulb. They receive the superior petrosal and occipital sinuses, the mastoid emissary veins and the diploic veins. They are usually involved with other sinuses. In event of blockage, there may be edema over the mastoid area and obvious venous distention; a positive Queckenstedt sign and papilledema may also be present.

5. The cavernous sinuses lie at the base of the skull flanking the sella turcica and communicate with many veins—the central retinal, the orbital, the sylvian and the inferior cerebral veins from the cortex. A maze of vessels communicate with one another through the circular sinus, emptying posteriorly into the superior and inferior petrosal sinuses, which, in turn, drain into the transverse sinuses and bulbs of the jugular veins, respectively. A distinctive picture is presented.

PATHOLOGIC PHYSIOLOGY

Free anastomoses exist between vessels of the face and sinuses in the space roughly defined by the nose and upper lip. The veins and

arteries freely communicate; the veins are without benefit of valves, and the whole area lacks adequate lymph node drainage. With infection of this area the only line of physiologic defense is a local pyogenic membrane. For this reason, the Hilton maneuver for opening deep abscesses should not be employed in operations on the nose, for to do so would break through the only normal defense, the pyogenic membrane. This is also the reason that extraction of a molar causes so much reaction, while abscesses about the tonsils are relatively innocuous. The thrombophlebitis which always accompanies an inflammatory reaction may spread retrogradely, and in these undefended areas may extend along veins between dehiscent or other bones to the cavernous sinuses. Usually, however, this extension is along the superior or inferior ophthalmic veins from connections with the ethmoidal, facial or temporal veins.

How a sinus thrombosis occurs is of interest. Most physicians fail to realize that any injury—whether from operation or accident, infected or not—is walled away from the surrounding healthy tissue by a zone of thrombosed vessels—minute though they may be—in a bog of inflammatory elements which occurs whether or not infection is present. These minute thrombi rarely have retrograde extension. They are more apt to extend if the area is infected, especially if the infection is caused by hemolytic Staphylococcus aureus. The thromboses of veins in an operative area are least apt to spread, but occasionally they do, even after a simple tonsillectomy.

A review of the clinical records of the patients in City Hospital, Cleveland, from 1921 to 1947 in whom involvement of the dural sinuses was observed is the subject of this paper.

Thromboses may be classified in two ways as (*a*) marantic (nonseptic) and (*b*) septic (infected or noninfected).

MARANTIC THROMBOSIS

Marantic thrombosis occurs in patients with debilitating conditions at any time during life, but usually in old age; it is not common in youth or middle life unless the patient has a long-drawn-out associated asthenic disease. This type might be the result of injury to the endothelial lining from bacterial or other toxins; changes in the blood which favor clotting, such as increased viscosity from dehydration and polycythemia, and slowing of the general circulation.

The symptoms and signs depend on the location and extent of the lesion and the presence or absence of satisfactory collateral circulation. Occlusion of a limited segment of a cerebral vein or dural sinus causes little circulatory disturbance. A small thrombus of this type may be an incidental observation post mortem. When destructive lesions do occur, they are extensive and are associated with or

closely followed by serious changes in the structure of the brain, congestion, edema and hemorrhage. The cerebrospinal fluid may be clear, xanthochromic or bloody; the amount of protein is usually elevated, and the number of lymphocytes may be slightly increased. The superior sagittal sinus is the one in which noninfectious thrombi are most likely to develop, probably because of the numerous lacunas and fibrous septums present. The straight sinus is reported to be next in frequency. Arteriosclerotic thrombosis may occur with its transient paralyses, but usually these attacks are ephemeral.

Eight of the 61 cases (2 probably) in our series were observed to be marantic in type (1 other was possibly of a marantic type); contrary to expectation, in all but 2 only the transverse sinus was involved. Four of these cases were of elderly patients with carcinoma and cranial metastases, and the thrombosis of the adjacent vessels was a finding which had given no symptoms or signs during life (cases 1 to 4 in the table).

One patient was a deformed and debilitated 10 year old white girl (case 5, M. L.) who had a symptomless marantic thrombus of the right transverse sinus, a large spina bifida, decubitus ulcers over the hip and back, bilteral chronic pyelonephritis and a large internal hydrocephalus with hydromyelia.

The right transverse sinus of a 65 year old Negro man (case 6, S. N.) was occluded by a sterile thrombus from an old fracture of the posteroinferior portion of the right parietal bone. He had no symptoms or signs of disturbed cerebral circulation.

A marantic thrombus was present in the transverse sinus of a 34 year old white man (case 7, L. K.), an admittedly heavy drinker who had complained of loss in weight of 10 pounds (4.5 Kg.) and continuous vomiting for more than two months. Immediately preceding his admission to the hospital he experienced sudden, sharp pain in the upper part of the abdomen and fell to the floor unconscious. There was no convulsion, and unconsciousness lasted about five minutes. The only significant positive observations on his admission were moderate malnutrition; a sluggish reaction of the pupils to light, inequality of the pupils, the left being larger than the right; the edge of the liver palpable 4 to 5 cm. below the costal margin, and a right inguinal hernia. The rest of the neurologic examination showed nothing abnormal. The urine gave a 2 plus reaction for albumin. He became stuporous and died within forty-eight hours. Autopsy revealed old bilateral thrombi of the transverse sinus, edema of the brain, congestion of the subarachnoid vessels, acute bronchitis, fatty infiltration of the myocardium and liver, acute splenic hyperplasia and right inguinal hernia.

The only nonseptic thrombosis of the cavernous sinus occurred in an elderly white man (case 8, C. H.), who was brought in to the hospital unconscious from his "seventh stroke" within a ten year period. He had an old spastic hemiparesis on the right side, evidence of arteriosclerosis, blood pressure of 250 systolic and 160 diastolic and a shortened right leg due to an old injury. Lumbar puncture yielded bloody fluid, but it was under no increased pressure. Urea nitrogen measured 58.5 mg. per hundred cubic centimeters.

The observations at autopsy were partially complete bilateral thrombosis of the cavernous sinuses and basilar plexus; multiple cerebral hemorrhage (right frontal lobe, right temporal lobe, left putamen and globus pallidus, with rupture

into the ventricle); mesencephalic hemorrhage; arteriolar and arterial nephrosclerosis; generalized arteriosclerosis; old complete thrombosis of the distal portion of the right circumflex branch of the right coronary artery with infarction; healed duodenal ulcer, and coxa vara of the right hip.

The "possible" instance of thrombus mentioned previously was that of a 51 year old Negro man who had a sudden onset of convulsions following pneumothorax for pulmonary tuberculosis. He was thought to have thrombosis of the superior sagittal sinus following air embolism, but permission for autopsy was not obtained. The convulsions were unilateral, involving the right foot and lower leg and, subsequently, the entire lower extremity. The patient did not lose consciousness during most of the convulsions. Later, convulsions gradually included the left foot and leg, and finally the right arm. Gradually increasing changes in the eyegrounds were observed over a thirteen day period, resulting in papilledema in the left eye and slight blurring of the right disk, dilatation of the veins bilaterally, retinal hemorrhage, slight chemosis and mild orbital edema. The spinal fluid was normal. The patient also had long-standing diabetes mellitus and hypertensive cardiovascular disease. This case is the only possible one in our series of marantic thrombosis of the superior sagittal sinus. Autopsies were performed in all cases in this group except this last one.

SEPTIC THROMBOSIS

To the symptoms that occur in patients with marantic thrombosis must be added those of infection, suppuration and involvement of the neighboring nerves in septic thromboses. Meningitis and abscesses of the brain result from direct extension from the involved sinuses; septicemia is initiated by the liberation of virulent bacteria and their products into the blood stream, and suppurative infarcts and scattered abscesses from portions of the infected clot disseminate all over the body. The reverse is also true—bacteremia may localize and produce all the signs of a primary septic thrombosis. Infection of dural sinuses is always secondary to infections elsewhere in the body.

Ford [2] stated that the transverse sinus is the one most commonly affected, and in the majority of cases the thrombosis is a sequela of otitis media with, or even without, mastoiditis. Since, as most authors have stated, the transverse sinus is the one most commonly involved, it follows that the ear as a focus should be the most feared. Such a fear is justified because the ear may give little or no indication of trouble and the focal symptoms may be hidden. The possibility of thrombosis of the transverse sinus with infection of the ear should always be kept in mind, especially since the ear may show little evidence of the severe involvement internally. One should always remember that an infection in or about the ear can result in such a complication, and perhaps the only sign of its existence will be edema of the area over the mastoid.

The spread of infection to the cavernous sinus was described by Grove,[3] who stated that the cavernous sinus through its afferent and

3. Grove, W. E.: Septic and Aseptic Types of Thrombosis of Cavernous Sinus, Arch. Otolaryng. **24**:29 (July) 1936.

Summaries of Cases of Thrombosis of Dural Sinuses

Case No. and Initials	Age, Sex and Race	Year Admitted to Hospital	Focus	Bacteria	Probable Method of Spread	Sinus Involved	Length of Illness	No. of Days in Hospital	Height of Fever, C.	Associated Disorders
					Marantic Thrombosis					
1 P. B.	69 yr. M White	1937	.....	None	.....	Left transverse	3 yr.	5	38	Carcinoma of neck; no symptoms referable to thrombosis
2 G. D.	46 yr. M White	1936	.....	None	.....	Left transverse (parietal thrombi)	Unknown	73	39	Carcinoma of bronchus; atelectasis; pulmonary abscess; cerebral metastases
3 F. L.	86 yr. M White	1936	.....	None	.....	Left transverse (parietal thrombi with tumor)	Unknown	4	39	Carcinoma of stomach with multiple metastases; bronchopneumonia; thrombosis of iliac artery; arteriosclerosis of coronary arteries
4 R. G.	60 yr. F White	1937	.....	None	.....	Left transverse	1 yr.	7	..	Carcinoma of colon with metastases to liver and lung; vegetations in aortic valve; infaret of spleen; thrombosis of femoral vein
5 M. L.	10 yr. F White	1930	.....	None	.....	Right transverse	Birth	67	39	Spina bifida; internal hydrocephalus; pyelonephritis; decubitus ulcers; hydromyelia
6 S. N.	65 yr. M Negro	1944	Fracture right parietal bone	None	Direct	Right transverse	Unknown	14	39.5	Acute and chronic pyelonephritis; bronchopneumonia
7 L. K.	34 yr. M White	1926	.....	None	Nasal infection	Transverse (bilateral thrombi)	60 days	2	42	Edema of brain; congestion of subarachnoid vessels; organizing thrombus of lateral sinus (old); acute bronchitis; fat infiltration of myocardium and liver; acute splenic hyperplasia; right inguinal hernia
8 C. H.	Elderly adult M White	1935	.....	None	.....	Cavernous parietal thrombi	10 yr.	4	39	Multiple cerebral hemorrhage (right frontal lobe, right temporal lobe, left putamen and globus pallidus with rupture into ventricle); mesencephalic hemorrhage; partial thrombosis basilar plexus; arteriolar and arterial nephrosclerosis; general arteriosclerosis; thrombosis distal right circumflex branch of right coronary artery with infarction; healed duodenal ulcer; coxa vara of right hip

9 S. K.	10 yr. M White	1925	Otitis media (right) and mastoiditis	Streptococcus pyogenes	Direct	Right transverse	14 days	2	41	Thrombosis of right jugular vein; pulmonary infarcts; bronchopneumonia
10 S. B.	21 yr. M White	1926	Meningitis	None	Direct	Right transverse	21 days	20	40.5	Multiple abscesses of the brain
11 R. B.	3 yr. F White	1928	Otitis media and mastoiditis	None	Direct	Transverse (bilateral thrombi)	13 days	1	41.4	Temporal and subperiosteal abscess; meningitis; thrombosis of both cavernous sinuses
12 S. B.	2 yr. M White	1929	Otitis media and mastoiditis	None	Direct	Right transverse and jugular bulb	21 days	18	41	Measles; scarlet fever; bronchopneumonia; pleurisy; thrombosis of torcular meningeal vessels over temporal lobe and in sagittal cerebellar tissue
13 D. Y.	4 yr. M White	1929	Otitis media and mastoiditis	None	Direct	Transverse (bilateral thrombi)	Unknown	1	40	Hyperemia of brain; bronchopneumonia
14 V. L.	68 yr. M Negro	1930	Otitis media and mastoiditis	None	Direct	Left transverse	177 days	176	41	Nephrosclerosis; bronchopneumonia; senile gangrene both legs; amputation
15 A. W.	51 yr. F White	1930	Meningitis	Streptococcus	Direct	Transverse (bilateral thrombi)	4 days	1	?	Spinal tap yielded 836 cells, 91 per cent polymorphonuclear leukocytes, ++++ Pandy reaction
16 J. B.	14 yr. F Negro	1932	Otitis media and mastoiditis	Beta hemolytic streptococcus	Direct	Right transverse	55 days	49	41	Spinal tap yielded normal fluid; localized meningitis; blood cultures produced streptococci
17 L. K.	3 mo. F White	1933	Bilateral otitis media	Blood culture negative	Direct	Left transverse	15 days	1	39.5	Meningitis; cerebral hemorrhage; thrombosis of great vein of Galen
18 K. H.	3 yr. F White	1934	Otitis media and mastoiditis	None	Direct	Right transverse	7 days	4	41	Pansinusitis; measles; bronchopneumonia
19 D. E.	2 yr. F White	1934	Otitis media and mastoiditis	Nonhemolytic streptococcus	Direct	Left transverse	23 days	17	40.5	Septicemia; bronchopneumonia; pulmonary abscess; atelectasis; spinal tap yielded 16 cells, 100 per cent mononuclear leukocytes
20 A. F.	27 yr. F White	1934	.....	.....	.....	Transverse (bilateral thrombi)	22 days	1	38	Spinal tap bloody; thrombosis of superior longitudinal sinus, cortical veins; necrosis of cerebral and cerebellar cortex; subarachnoid hemorrhage; mild acute leptomeningitis
21 W. G.	19 mo. M White	1937	Otitis media and bilateral mastoiditis	None	Direct	Transverse (bilateral thrombi)	17 days	17	39	Meningitis; spinal tap yielded 6,800 cells, ++++ Pandy reaction; thrombosis of superior sagittal sinus, all cerebral veins; severe cerebral necrosis; hemorrhage right hemisphere with rupture into lateral ventricle; stenosis of cerebral aqueduct by external pressure; internal hydrocephalus

Summaries of Cases of Thrombosis of Dural Sinuses—Continued

Case No. and Initials	Age, Sex and Race	Year Admitted to Hospital	Focus	Bacteria	Probable Method of Spread	Sinus Involved	Length of Illness	No. of Days in Hospital	Height of Fever, C.	Associated Disorders
Septic Thrombosis of Transverse Sinus—Continued										
22 S. R.	72 yr. M White	1936	Osteomyelitis of right mastoid	Pneumococcus	.....	Right transverse	?	1	40	Suppurative meningitis; septicemia with multiple abscesses; spinal tap yielded 290 cells, 100 per cent polymorphonuclear leukocytes, ++++ Pandy reaction, pneumococci
23 C. G.	40 yr. M White	1930	.....	.....	.....	Transverse (bilateral thrombi)	?	8	40	Localized meningitis; spinal fluid xanthochromic; multiple cerebral hemorrhages; old fracture of base of skull; infarcts of lungs; thrombosis of superior sagittal sinus
24 R. V.	2 yr. F White	1935	Bilateral otitis media and mastoiditis	Streptococcus	Direct	Left transverse	36 days	36	40	Thrombosis of superior sagittal sinus; general purpura of skin
25 S. H.	14 mo. F White	1936	Bilateral otitis media	H. influenzae	Direct	Left transverse	14 days	1	39.5	Meningitis; spinal fluid yielded 2,000 polymorphonuclear leukocytes, ++++ Pandy reaction; H. influenzae; bronchopneumonia
26 N. Y.	6 yr. F White	1936	Bilateral otitis media and mastoiditis or pharyngitis	Hemolytic streptococcus	.....	Left transverse	21 days	9	40.5	Thrombosis of superior sagittal sinus; septicemia; suppurative arthritis of right hip; cellulitis of right hip; septic infarcts of spleen; acute glomerulonephritis; hemorrhagic cystitis; mastoidectomy (right side)
27 R. O.	6 yr. M White	1936	Right otitis media and mastoiditis	Hemolytic streptococcus	Mastoid, ear	Right transverse	96 days	92	40.5	Meningitis; scarlet fever; thrombosis of superior sagittal sinus; mastoidectomy (right side)
28 W. C.	12 yr. M White	1938	Right otitis media and mastoiditis	Streptococcus; Escherichia coli; Proteus vulgaris	Direct	Right transverse	13 days	11	42	(Symptoms of thrombosis of cavernous sinus) thrombosis of transverse sinus confirmed by operative observations; pneumonia, treated with sulfanilamide; no autopsy performed
29 S. H.	14 yr. F White	1940	Left otitis media and mastoiditis	Str. viridans	Direct	Transverse (bilateral thrombi)	24 days	10	40.5	Meningitis (spinal tap yielded 1,400 cells, 98 per cent polymorphonuclear leukocytes, ++++ Pandy reaction, St. viridans); tonsillitis; cervical lymphadenitis; bronchopneumonia; thrombosis of cavernous, inferior and superior petrosal sinuses, left internal jugular vein; chronic sphenoidal sinusitis, treated with sulfanilamide, sulfapyridine, "promin"

R. W.	M White		and mastoiditis			verse				treated with sulfanilamide; patient died during mastoidectomy (right side); thrombosis confirmed by operation; no postmortem examination
31 J. T.	4 mo. M White	1934	Meningitis	Meningococcus	Direct	Right transverse	107 days	104	40	Chronic leptomeningitis; chronic internal obstructive hydrocephalus; ependymitis granularis
32 G. M.	26 yr. M White	1935	Otitis media and mastoiditis	Str. viridans	Otitis media; mastoiditis; thrombosis; septicemia; endocarditis	Right transverse	36 days	21	41.2	Streptococcic septicemia; acute vegetative endocarditis of mitral valve; localized encephalitis; acute suppurative meningitis with small amount of subarachnoid hemorrhage; acute local glomerulonephritis with acute focal suppurative glomerulitis; acute infarct and hyperplasia of spleen; multiple petechial cutaneous hemorrhages; condensing osteitis of both mastoids; phlebectasia and partial thrombosis of veins of prostatic plexus
33 E. S.	40 yr. M White	1929	Syphilitic meningitis	.....	Direct	Left transverse	.....	10	40	Syphilitic aortitis (ascending aorta); chronic syphilitic meningitis; edema of brain; thrombosis of superior sagittal sinus; congenital anomaly of pulmonary valve; dilatation of heart; bronchopneumonia
34 E. B.	40 yr. F White	1937	Chronic meningitis	None	Direct	Right transverse	6 yr.	66	41.5	Recurrent astrocytoma in right frontoparietal region (partially removed surgically January 1935); meningomyelocele; remote surgical scar in right frontoparietal region with defect of cranium; thrombosis of straight venous sinus; chronic leptomeningitis
				Septic Cavernous Sinus Thrombosis						
35 D. B.	16 yr. F White	1926	Pustule on nose	?	Direct	Bilateral cavernous	9 days	4	41.5	Meningitis; pulmonary infarcts; abscesses of kidneys; purulent hemorrhagic cystitis; bronchopneumonia
36 L. D.	14 yr. M White	1927	Maxillary sinusitis	Staphylococcus	Direct	Right cavernous	30 days	9	41.2	Maxillary sinusitis (right) five days prior to death; typhoid; staphylococcic septicemia; typhoid ulcers in ileum and cecum; infarcts of lungs; pleurisy
37 R. B.	66 yr. M White	1935	Ethmoiditis, sphenoiditis	Streptococcus	Direct right, then left cavernous sinus	Bilateral cavernous	14 days	6	41	Bronchopneumonia; Laennec's cirrhosis; splenomegaly; ascites; esophageal varices with hemorrhage into upper part of gastrointestinal tract

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Summaries of Cases of Thrombosis of Dural Sinuses—Continued

Case No. and Initials	Age, Sex and Race	Year Admitted to Hospital	Focus	Bacteria	Probable Method of Spread	Sinus Involved	Length of Illness	No. of Days in Hospital	Height of Fever, C.	Associated Disorders
Septic Thrombosis of Transverse Sinus—Continued										
38 J. F.	66 yr. M White	1935	Right otitis media and mastoiditis	Streptococcus	Tympanic antrum; mastoid; meningitis; thrombosis	Bilateral cavernous	21 days	1	41.8	Thrombosis of basilar plexus; meningitis (spinal fluid yielded 32,000 cells, all polymorphonuclear leukocytes, ++++ Pandy reaction); suppuration of right middle ear, tympanic antrum; mastoid erosion of tegmen tympani with sinus to lateral ventricle; chronic lymphoid leukosis; bronchopneumonia; chronic ethmoiditis; nasal polyps
39 G. P.	12 yr. M White	1936	Osteomyelitis of femur or septicemia	Staphylococcus albus	Osteomyelitis; septicemia; septic thrombosis of cavernous sinus	Cavernous	10 days	5	40	Osteomyelitis of left femur; septicemia; septic infarct of left occipital lobe; focal acute exudative encephalitis
40 H. K.	50 yr. M Negro	1945	Tooth extraction-inferior 2d left molar	Hemolytic streptococcus	Thrombophlebitis of emissary vein, cavernous sinus	Cavernous	14 days	1	42.3	Thrombophlebitis of arachnoid veins of cerebrum and straight sinus; inflammation of internal carotid artery, semilunar ganglion and surrounding tissue; pulmonary infarcts; treated with sulfadiazine and penicillin intramuscularly and intrathecally
41 G. K.	28 yr. M White	1938	Ethmoid sinusitis (right)	Pneumococcus type 3	Direct to cavernous sinus; meningitis; septicemia	Cavernous	2 days	8 hr.	42	Meningitis (spinal fluid yielded 3,000 cells, 100 per cent polymorphonuclear leukocytes, ++++ Pandy reaction); pneumococcus type 3 septicemia; bronchopneumonia; local necrosis of lenticular nucleus; pulmonary infarcts; treated with azosulfamide
42 N. T.	19 yr. M White	1941	Sinusitis with tooth extraction	Staphylococcus aureus	Paranasal sinus by direct extension	Cavernous	11 days	1	40.8	Purulent ethmoidal, sphenoidal, frontal sinusitis; panarteritis right internal carotid artery; local meningitis; encephalomalacia of anterior portion right temporal lobe; multiple septic infarcts (pulmonary) with abscesses; septicemia; treated with sulfathiazole
43 A. H.	50 yr. M Negro	1941	Pustule upper lip	Staph. albus	Cellulitis of face and orbit, cavernous sinus; meningitis	Cavernous	9 days	2	41.2	Meningitis (spinal fluid yielded 5,700 cells, 95 per cent polymorphonuclear leukocytes, ++++ Pandy reaction); focal suppurative pneumonitis and pleurisy; periportal hepatitis; en-

P. N.	M White	1936	Frontal ethmoid sphenoid sinusitis	Pneumococcus type 3	Direct to meninges to superior longitudinal sinus	Superior longitudinal	6 days	1	39.8	Meningitis (spinal fluid yielded 6,600 cells, 100 per cent polymorphonuclear leukocytes, ++++ Pandy reaction); paranasal sinusitis (sphenoidal, ethmoidal and frontal); subdural hemorrhage over right frontal and parietal lobes of cerebrum
45 J. W.	6 mo. F White	1937	Meningitis	H. influenzae	Direct	Superior longitudinal	10 days	8	40.4	Meningitis (spinal fluid yielded 7,500 cells, 100 per cent polymorphonuclear leukocytes, ++++ Pandy reaction); necrotizing arteritis of basilar artery with partial thrombosis; treated with sulfanilamide
46 W. A.	1½ yr. M White	1938	Meningitis	H. influenzae pneumococci	Direct	Superior longitudinal	9 days	4	40.5	Meningitis (spinal fluid yielded 400 cells, 86 per cent lymphocytes, — Pandy reaction); infection with Ascaris lumbricoides; treated with sulfapyridine, sulfanilamide
47 J. S.	15 mo. M White	1927	Infection of upper respiratory tract; pneumonia	.....	Respiratory infection; pneumonia; meningitis; sinus thrombosis	Superior longitudinal	17 days	6	41.2	Meningitis (spinal fluid yielded 1,600 cells, 90 per cent polymorphonuclear leukocytes, + Pandy reaction); bronchopneumonia; abscess in lower lobe of right lung; pleurisy; cerebral hemorrhage; posterior horn of left lateral ventricle filled with clotted blood
48 T. H.	6 yr. M White	1935	Fracture of skull	Pneumococcus	Nasal passage to fracture-site to meninges	Superior longitudinal	6 days	2	40	Meningitis (spinal fluid yielded 1,600 cells, 98 per cent polymorphonuclear leukocytes, ++++ Pandy reaction); complete fracture of left orbital plate of frontal bone; capillary fracture, extension to cribriform plate of ethmoid bone and left small and great wings of sphenoid bones with local hemorrhage
49 V. C.	8½ mo. F White	1936	Pyemia from mastoid or eczema	Hemolytic streptococcus	Pyemia	Superior longitudinal and cerebral veins	79 days	64	40.5	Pyemia; osteitis of mastoid antrums; suppurative arthritis of left hip and sacroiliac joint; osteomyelitis of head of left femur; bronchopneumonia; infarcts in right lung
50 H. P.	14 mo. M White	1939	Bilateral otitis media	Staph. albus; Bacillus subtilis	.....	Superior longitudinal and cerebral veins	7 days	3	39.5	Bilateral otitis media; thrombosis of superior cerebral veins; suppurative meningoencephalitis of right frontal and temporal lobes; chickenpox; (spinal fluid yielded many red blood cells, ++++ Pandy reaction, fluid opalescent)

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efferent venous channels is brought into close relation with the tonsils, the soft palate, the pharynx, the posterior portions of the superior and inferior alveolar arches, the face, the orbit, the nose and all its sinuses, the ear and the mastoid. In our experience, the ethmoidal empyemas or the infections with thrombotic ethmoidal veins, extending along the ophthalmic veins to the cavernous sinuses, are the commonest causes of these thromboses.

This involvement of the cavernous sinus is sometimes due to extension anteriorly of the thrombosis of the transverse sinus or to extension from thrombophlebitis in any of the afferent or efferent veins of the cavernous sinus. Infection of this sinus also may be due to spread by the lymphatics, nerve sheaths, thrombosed arteries, fascial planes, bony dehiscences and bacteremia, and by direct extension from basilar meningitis, abscess in the postorbital space, suppurative sphenoiditis, suppuration of the petrous portion of the temporal bone and suppuration of the frontal bone as a result of frontal sinusitis. Septic thrombi

Fig. 1.—*A* shows late bilateral ethmoiditis, frontal sinusitis and thrombophlebitis of superficial veins of forehead in a 2½ year old boy, while *B* shows the lesion ten days later, after treatment.

of the superior sagittal sinus most frequently result from septicemia and meningitis.

In all septic thrombi of the dural sinuses, staphylococci, streptococci and pneumococci (frequently Hemophilus influenzae in infants) are the usual causative organisms.

Transverse Sinus—Of the 61 cases reviewed, 30 were of septic thromboses of the transverse sinus. In 19 cases the thrombosis developed from otitis media with mastoiditis; in 2, from otitis without mastoiditis (case 17, L. K., an infant 3 months of age, and case 25, S. H., a 14 month old infant); in 5, as a sequel to meningitis; in 1, from osteomyelitis of the mastoid without evidence of otitis (case 22, S. R.), and in 1, from either otitis or a severe suppurative pharyngitis which occurred concomitantly with severe edema and thrombosis of the internal jugular vein (case 26, N. Y.); in 2 cases the thrombosis was of unknown origin. The ages of the patients ranged from 3 months to 72 years, but only 9 of the 30 patients were more than 14 years old. Thrombosis was bilateral in 7 cases; meningitis was a

sequel in 11. Thrombosis of other sinuses was associated with this involvement in 11 cases. In 1 case (case 21, W. G.) of bilateral thrombosis of the transverse sinus, the great vein of Galen, the superior sagittal sinus and all the cerebral veins showed extensive thrombosis and organization, with severe necrosis and hemorrhage of the right cerebral hemisphere and rupture into the lateral ventricle. There were associated edema of the brain, stenosis of the cerebral aqueduct by external pressure and moderately severe internal hydrocephalus.

Only 4 patients in this group lived. Autopsies were performed on all but 2 of the others; in these 2, thrombosis was observed at mastoidectomy. Only 3 patients died in 1939 from septic thrombosis of the transverse sinus, and we have records of only 2 deaths between 1940 and 1947 proved by necropsy to be due to this condition. Symptoms of sepsis were present in almost every case, and approximately 60 per cent showed evidence of meningeal irritation and increased intracranial pressure. The 4 patients surviving were all treated after 1938.

Fig. 2.—*A*, ethmoid sinusitis (scarlet fever) in a young woman; *B*, the lesion one week later, after treatment by nasal drainage.

Cavernous Sinus.—Because of its strategic location, the signs and symptoms of thrombophlebitis in this sinus are spectacular. The classic observations are chills, fever, severe prostration, leukocytosis and blood cultures yielding pathogenic organisms, usually with evidence of infection about the head and face. There are unilateral edema of the orbital tissues, usually limited to the eyelids and starting about the inner canthus, congestion of the veins above the eye, chemosis, proptosis, congestion of retinal veins, retinal hemorrhages and often congestion and edema of the optic disks. The third, fourth and sixth cranial nerves are usually paralyzed, and a cadaveric, immobile lack-luster eye is produced. Not infrequently, the upper branch of the fifth nerve may be involved. The process extends to the opposite side by way of the circular sinus within a few days, and the opposite eye begins to show the same changes. Meningitis frequently follows.

In addition to the 3 cases described previously in association with thrombosis of other sinuses, our records show 14 patients who died with septic thrombosis of the cavernous sinuses between 1926 and 1942.

One patient (case 39 G. P.) in this group was 12 years old, and 2 were 14 years of age. All the rest were above 15, and the majority were more than 30 years of age. We have records of only 2 deaths from septic thrombosis of the cavernous sinus during the period from 1942 to 1947, since the advent of sulfonamide drugs and antibiotics.

The histories, symptoms and findings were similar for all of these persons. The original infection and subsequent progressive involvement in these patients is described briefly in the following typical case.

CASE 35.—D. B., a 16 year old white girl had onset with a small pustule on the nose which was opened with a finger nail. It became larger five days later. There developed edema and redness of that side of the face and eyelid, headache and a septic type of fever, with unilateral orbital signs. The opposite eye became involved within thirty-six hours, with meningeal signs. She died within two weeks of the initial trauma. The pathologic report was thrombosis of the cavernous sinuses, meningitis, multiple infarcts of both lungs and pyemic abscess of both kidneys.

Fig. 3.—*A*, postscarlatinal ethmoiditis in a 4 year old girl. Treatment consisted of a wick in the nostrils, with epinephrine packs applied for fifteen minutes four times a day; *B* shows the result one week later, after nasal drainage.

The other patients had similar signs and symptoms, varying only in the degree, the location of the original area of infection, the route and the extent of spread. The infections which preceded involvement of the cavernous sinus were infection of the upper respiratory tract, with erysipelas of the face (2 cases); pustules of the upper lip, face or nose (4 cases), and (1 case each) ethmoid and sphenoid sinusitis (case 37, R. B.), ethmoid sinusitis (case 41, G. K.), maxillary sinusitis with irrigation (case 36, L. O.), sinusitis with tooth extraction (case 42, N. T.), tooth extraction with infection of upper respiratory tract (case 40, H. K.), septicemia or osteomyelitis of the left femur (case 39, G. P.) and purulent ethmoiditis with otitis and mastoiditis (case 38, J. F.). During the course of typhoid in a 14 year old boy (case 36, L. O.) there developed purulent maxillary sinusitis and subsequently thrombosis of the cavernous sinus. He died five days after the diagnosis of maxillary sinusitis was made.

All the patients whose cases have been described died. Autopsies were performed in 9 of the 14 cases, and observations are outlined in the table.

As regards foci of infection, it is a fact that a commoner potential cause of thrombosis is infection occurring in the ethmoid and sphenoid sinuses rather than infection of the mastoid. These clinical conditions do not always go on to thrombosis of the cavernous sinus, but the threat of spread is there. Unlike infection of the mastoid, the objective evidence of disease is to be noted very early, and something may be done about it at once. It is our impression that many persons have ethmoiditis and sphenoiditis in comparison with the few who have infections of the middle ear, and mastoid; but objective signs of the latter conditions are easily missed so that treatment is not given; as a result, comparatively more patients have thrombosis of the transverse sinus.

The number of cases of infection of the nasal accessory sinuses recorded at City Hospital between 1921 and 1938 was 1,316. Prior to 1938, these cases were not accurately classified as to the nasal sinus

Fig. 4.—*A*, ethmoiditis in a 4 year old girl; *B*, the lesion one week later, after nasal drainage.

involved, but between 1938 and 1946 there were 137 recorded cases of ethmoiditis. In our opinion, this is probably the commonest condition creating the scene for thrombophlebitis.

Since 1922, for treatment of sinusitis we establish medical drainage with epinephrine packs, postural drainage and local application of lightweight hot packs to the swollen lids. Most of the patients recovered before thrombosis of the cavernous sinus developed, even before the days of sulfonamide drugs and penicillin.

A spread from the nose (usually from the ethmoid sinus) may cause secondary swelling at the inner canthus with rapid involvement of both eyelids. Operation at this early stage may cause a fulminating type of reaction, and even death. It is for this reason that medical means have been employed to establish drainage of the ethmoid sinuses, with the hope that the secondary lesion would be aborted if the primary lesion were drained.

With the beginning of edema of the eyelids at the inner canthus, the sharp orbital lines are smoothed out, and fever and often signs of sepsis

are present. When the eyeball is examined at this stage, it is observed to be mobile in every direction, and the eyegrounds are normal. The conjunctiva is usually clear, although there may be slight involvement of the tarsal area.

Roughly, the lesions about the eye may be found in the front, in the area of the lid, in the back or at the side of the eyeball or inside the eye itself. Many untreated lesions go on to abscess formation. If the

Fig. 5.—Left, ethmoiditis resulting from cervical adenitis (scarlet fever) in a 4 year old girl. Right, the affected region one week later, after treatment by nasal drainage.

lesion remains localized to the eyelids, the prognosis is usually good when the simple regimen outlined previously is followed. If the lesion is at either side of the eye, the prognosis, though not hopeless, is less favorable, for extensive thrombophlebitis may occur. If the lesion is posterior

Fig. 6.—Abscess in eyelid resulting from acute ethmoid and maxillary sinusitis, acute otitis media and acute cervical adenitis (scarlet fever).

to the eyeball or in the eyeball itself, secondary involvement of the ophthalmic veins and secondary extension, with thrombophlebitis to the central cranial veins, are apt to follow. If thrombosis occurs, all the signs of this condition develop.

The pathologic changes in this type of case were described in detail by Lederer.[4]

4. Lederer, F. L.: Fulminant Sinus Disease: Study of the Pathogenesis, Surg., Gynec. & Obst. **60**:645 (March) 1935.

Superior Sagittal Sinus, Inferior Sagittal Sinus and Straight Sinus.—Septic thromboses in these sinuses are much less frequent than in the transverse and cavernous sinuses. They may result from retrograde spread from the transverse sinuses, but in most instances they are a complication of leptomeningitis. In our series, in addition to the cases mentioned previously as occurring with thrombosis of the transverse or cavernous sinus, there were 7 instances of septic thrombosis of the superior sagittal sinus. There were no instances of septic involvement of the inferior or the straight sinus existing alone. Of the 7 cases, thrombophlebitis in the superior sagittal sinus developed in 5 as a result of meningitis. Brief résumés follow:

CASE 44.—P. N., a 13 year old white boy, had a typical history and clinical signs of meningitis. The culture of the spinal fluid yielded pneumococcus type 3; necropsy revealed thrombophlebitis of the superior sagittal sinus and superior cerebral veins, with subdural hemorrhage of the right frontal and parietal lobes.

CASE 45 (1937).—J. W., a 6 month old white girl, had meningitis due to H. influenzae. Postmortem examination showed a thrombosis of the superior sagittal sinus and hyperemia of the brain, but no actual gross hemorrhage.

Fig. 7.—Ethmoiditis in a 3½ year old girl before treatment (*A*) and after treatment (*B*).

CASE 46 (1938).—W. A., an 18 month old white boy, had clinical signs almost identical with those in case 45.

CASE 47 (1927).—J. S., a 15 month old white boy, had infection of the upper respiratory tract and bronchopneumonia, followed by purulent meningitis of undetermined origin. Autopsy revealed thrombosis of the superior sagittal sinus, hyperemia of the brain and hemorrhage of the left side of the midbrain extending from the cortex to the caudate nucleus; several small hemorrhagic areas were in the internal capsule; the third ventricle and the posterior horn of the left lateral ventricle were filled with clotted blood.

CASE 48 (1935).—T. H., a 6 year old white boy, had pneumococcic meningitis and secondary thrombophlebitis of the sagittal sinus as a result of fracture of the skull. Autopsy revealed a complete fracture through the left orbital plate of the frontal bone, with extension by capillary fractures to the cribriform plate of the ethmoid and the left small and great wings of sphenoid bones with slight local hemorrhage. The superior sagittal sinus showed a septic thrombosis.

CASE 49 (1946).—V. C., an 8½ month old white girl, had chronic bilateral otitis media with development of pyemia. Autopsy showed osteitis of both mastoid antrums, suppurative arthritis of the left hip and sacroiliac joint; acute

osteomyelitis of the head of the left femur, suppurative thrombosis of the superior sagittal sinus and superior cerebral veins, bronchopneumonia and infarcts of the right lung.

CASE 50 (1939).—H. P., a 14 month old white boy, had bilateral acute purulent otitis media following chickenpox. Two days before his admission, and during his three day course in the hospital, he had left-sided convulsions, which later became generalized, with signs of meningeal and cerebral irritation. Autopsy revealed bilateral otitis media and thrombophlebitis of the superior sagittal sinus and superior cerebral veins, with suppurative meningoencephalitis of the right frontal and temporal lobes. The transverse sinuses were clear, and there was no evidence of direct spread of infection to the superior sagittal sinus.

The decided drop in incidence of septic thrombi of the dural sinuses after 1943 is attributed to the control of the predisposing infections by the use of combined sulfonamide drugs and penicillin.[5]

Fig. 8.—Cavernous sinus thrombosis in a 17 year old youth. Photographs were made one day before death of the patient.

SUMMARY

The anatomy of the dural venous sinuses is briefly reviewed in an effort to demonstrate the relation of lesions in this network to signs and symptoms produced clinically.

The marantic and septic types of thrombosis of the dural sinuses are discussed separately.

The lesions of patients with thrombosis of the dural sinuses at City Hospital, Cleveland, between and including the years 1921 and 1947 (61 cases) are described and defined as to the pathogenesis, type and associated pathologic conditions.

The most frequent causes of thrombi and their usual sites are demonstrated, and the findings in our series agree in general with those described in the extensive literature on the subject.

3395 Scranton Road (9).

5. Fox, S. L., and West, G. B., Jr.: Thrombosis of Cavernous Sinus: Newer Concepts in Its Management and Report of Three Cases, J. A. M. A. **134**:1452 (Aug. 23) 1947.

TREATMENT OF ACUTE INTUSSUSCEPTION BY AN ENEMA OF ROENTGENOLOGIC CONTRAST MEDIUM

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THE CONSERVATIVE treatment of intussusception in children has been a subject of interest for many years in the Scandinavian countries. Hirschsprung, Wichmann, Kock and Oerum and Monrad made important contributions to the treatment of this condition. It was from Sweden that the first report of the use of an enema of roentgenologic contrast medium in the treatment of intussusception in children was received. Olsson and Pallin [1] recorded the first successful results of such therapy in 1927, and similar reports came almost simultaneously from Retan in America and Pouliquen and his associates in France.

Whereas previous therapy had been almost exclusively surgical, these reports of the use of roentgenologic contrast medium, not only in diagnosis but also as therapy, reawakened interest in the conservative treatment. The method has gained much ground, and in this connection reference to Nyborg's [2] detailed study of the subject (1943) is of value.

It appears that the treatment of typical intussusception in children by the use of an enema of roentgenologic contrast medium is not generally familiar. Therefore, we wish here to give a short account of our procedure in treatment of standard material, in which we have attempted to master the conservative method, with special attention to the details of roentgenologic technic.

Our material included all the 18 cases of intussusception in children under the age of 3 years, who were uniformly examined and treated, in the hospital during 1944, 1945 and 1946. It has been established by many authors that acute intussusception occurs most frequently in early childhood. Seventy per cent of Nyborg's cases occurred in children under 2 years of age and 50 per cent in infants.

From the Department of Pediatrics (Dr. Lindberg) and the Department of Roentgenology, Norrköping Hospital.

1. Olsson, I., and Pallin, G.: Acta chir. Scandinav. **61**:371, 1927.
2. Nyborg: Acta chir. Scandinav. (supp. 80) **89**:9, 1943.

In our material there were 2 cases in children aged 5, in addition to the 18 under 3 years of age. Of the 18 patients, 9 were infants (table).

According to Wichmann's simplified terminology for the classification of intussusception in children, there was in our material no case of intussusception of either the small intestine or the colon, but in all 18 intussusception occurred at the boundary of the small intestine and the colon.

DIAGNOSIS OF INTUSSUSCEPTION

From the point of view of symptomatology, our material showed clearly the uniformity of the early stages and development of the dis-

Data on 18 Patients with Intussusception Treated by Means of Roentgen-Contrast Enema

Case No.	Sex	Age, Mo.	No. of Days Under Supervision	Duration of Symptoms, Hr.	Vomiting	Palpable Tumor	Blood in Feces	Reduction		
								Easy	Difficult	Narcotic Needed
1	M	12	2	1	—	+	—	..	..	+
2	M	8	1	12	+	+	—	..	..	+
3	M	18	3	6	+	+	—	+	..	..
4	M	15	5	2	+	+	+	..	+	..
5	F	9	3	6	+	+	—	+	..	..
6	F	17	3	2	+	+	—	..	..	+
7	F	18	2	3	+	+	—	+	..	..
8	F	7	1	3	—	+	—	+	..	..
9	F	10	..	5	—	—	—	+	..	..
10	M	9	4	8	+	+	—	+	..	..
11	F	5	2	6	+	+	+	+	..	..
12	M	30	2	6	+	+	—	+	..	..
13	F	6	2	12	+	+	+	+	..	..
14	M	8	2	12	—	—	—	+	..	..
15	M	13	6	2	—	+	—	+	..	..
16	M	27	2	3	—	+	—	+	..	..
17	M	12	?	1	+	+	—	+	..	..
18	M	25	4	5	+	—	—	..	+	..

ease. In almost every case the initial symptoms appear suddenly. A violent pain in the abdomen causes the child to scream. This cry is unlike the normal scream of a child. It has an anguished and ominous character that frequently makes a strong impression on the mother. The child usually draws its legs up toward the abdomen, and in some instances presses its hands against the right side of the abdomen. Vomiting usually occurs with the first attack of pain. The attacks of pain soon affect the child's general condition in that clear signs of peritoneal shock appear. The child becomes pale, its expression suffering, its eyes vacant and fearful and its muscles relaxed. The initial attack lasts only a short time, but pain occurs intermittently at longer or shorter intervals, although these later attacks are considerably milder

than the first attack. During the intervals the child is obviously apathetic and usually somewhat lethargic. In the early stages of some cases diarrhea occurs, which can mislead diagnosis. Later, slime mixed with blood is discharged through the anus; this is to be regarded as a pathognomonic symptom of intussusception. In our opinion, however, this symptom should not be relied on for diagnosis, as it does not occur until the disease has reached a somewhat advanced stage. Nyborg stated that in only 36 per cent of his cases was blood discharged before twelve hours, and we observed this symptom in only 3 instances. This low incidence is due to the fact that our patients

Fig. 1.—Roentgenograms showing typical pictures of intussusception, *A*, in the transverse part of the colon and, *B*, in the ascending portion.

were available for treatment in the initial stages, none later than fourteen hours after the first sign and in most after the elapse of only a few hours.

The presence of a palpable intussusception tumor in the abdomen is often regarded as a fourth cardinal symptom. This symptom was apparent in 15 of our 18 cases and must, therefore, be regarded as of considerable importance. As these children are always in a condition of shock with abnormally relaxed abdominal muscles, palpation is easy.

The most important symptom, however, is the roentgenographic picture obtained by means of contrast enema. As soon as the presence of an intussusception is suspected, the child is subjected to a roentgenologic examination.

The roentgenologic examination shows a typical picture. The contrast medium passes with ease into the distal parts of the colon and reaches the intussusception, which is usually in the central region of the colon. The typical picture of the obstruction in the colon is similar to a figure 3, the joint between the two hooks being often weakly formed. The upper and lower segments equal the distance between the wall of the colon and the middle portion, and the weakly showing joint equals the volume of the intestine. In most cases the tumor can be seen to be pushed in an oral direction by the colon enema, and diagnosis can be based on the typical picture of the obstruction, together with its tendency to be dislodged (fig. 1).

The diagnosis of an acute intussusception of the type present in our material is easy in most cases. The history of the sudden onset of the condition, the presence of signs of abdominal shock in the child, the palpable tumor and the roentgenographic appearance are of great importance. The discharge of red-tinged slime through the anus is a sign appearing so late in the course of the disease that the diagnosis can be made long before the appearance of this ominous symptom.

METHOD OF REDUCTION

As soon as the diagnosis has been established, we proceed to the attempt to reduce the intussusception by means of the contrast medium used for roentgenologic diagnosis. Here it is of importance that the contrast medium be of the correct temperature, consistency and pressure. At this hospital, the medium is made of pharmabaryt[3] (1 Kg. [2.205 pounds] to 1.25 liter [2.2 pints]) water at a temperature of 37 C. (98.6 F.). The enema is poured from a position about 1.5 meters (about 5 feet) above the level of the patient. No alkali or other material to render the mixture smoother is added to the enema. The examiner controls the flow of the contrast medium by means of a clip on the rubber tube. The medium is allowed to flow until the obstruction is reached; a roentgenogram of the intussusception is then taken. Slowly, the colon is filled and the intussusception pushed in an oral direction. The colon is usually irritated and contracts as in cramp, thereby pushing back the contrast medium and practically emptying the intestine. It is important to cut off the flow of the enema until the contraction has ceased, when it can be renewed. Sometimes it appears as though the oral movement has ceased as a result of the contraction of the outer tube, and it is best to pause until the intestine has relaxed.

3. The composition of pharmabaryt® is 98 per cent barium sulfate and 2 per cent indifferent colloids.

As far as possible, one should avoid the use of manual action, since this tends to increase the irritation of the colon. With this procedure, it is usually possible to press out the intussusception to the region of

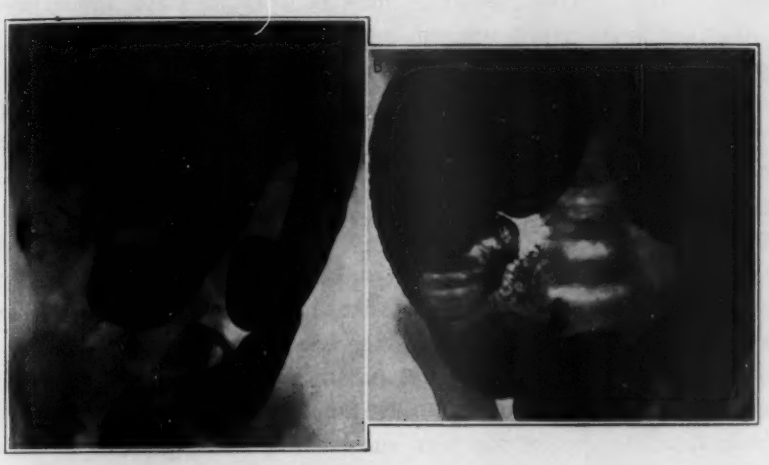

Fig. 2.—Roentgenograms showing the intussusception reduced to the beginning of the colon.

Fig. 3.—Roentgenograms showing *A*, a small part of the obstruction still remaining in the cecum, and *B*, the full reduction of the intussusception in the cecum and the contrast medium pouring freely into the small intestine.

Bauhin's valve and even to reduce it altogether. Reduction may be considered complete only when the contrast medium passes freely on into the small intestine. Unfortunately, it frequently happens that a

part of the obstruction about the size of a walnut remains in the cecum. One is forced to remove this manually. This is done by holding the movable cecum with one hand while massaging in an oral direction with the other. This procedure may be continued for about fifteen minutes. Should it not succeed, a pause of ten to fifteen minutes is advised to allow both the patient and the colon to relax. A renewed attempt should then prove successful. If this is not the case, the patient must be anesthetized (which is done easiest with ether); then the attempt is practically always successful. One can both see and feel the intussusception disappear; there is a sudden jerk and the contrast medium flows out into the small intestine. The patient also reacts noticeably; instead of screaming, twisting and turning as during examination, he becomes quiet and usually falls asleep. This does not occur, of course, if a narcotic has been used, but when these symptoms are observed during the removal of an intussusception, even though contrast medium does not flow out into the ileum, one can be almost certain that the attempt has been successful. Those patients in whom, even with the help of a narcotic, positive results have not been obtained will have to be treated surgically. No complication as a result of the enema treatment has been observed at subsequent operations.

COMMENT

The reduction of the intussusception by means of an enema of roentgenologic contrast medium was definitely successful in all our 18 cases, and this may prove the value of the method. Our results depend, of course, on several factors. All cases of intussusception are not reducible by this method. The strictures especially responsive to this treatment are those arising at the boundary between the small intestine and the colon, and our material consisted only of such cases. Furthermore, the time elapsed after the onset of the symptoms in 5 cases was one to two hours, in 3 cases three hours, in 6 cases four to six hours and in 4 cases eight to twelve hours. All the children were in good condition, and there was no objection either to forced attempts to reduce the intussusception or, in the difficult cases, to the use of a narcotic. The intussusception develops rapidly in most instances, and the swelling of the intestinal wall becomes greater the longer treatment is delayed. Our patients have, so far, been in a fortunate position as regards the time most favorable for treatment with the roentgenologic contrast medium. This is mainly due to the high percentage of all children below the age of 2 years who are under continual supervision at health centers. These centers provide constant care by specially trained nurses and pediatricians under the supervision of the government. In

Norrköping, more than 90 per cent of the 1,400 infants born yearly are under such supervision.

Other factors contributing to our favorable results are the manner of proceeding in the attempts at reduction, which were related in detail previously, and the use of narcotics in the cases otherwise resistant to reduction. In 3 of our 18 cases reduction was impossible without the use of general anesthesia. Several authors disapproved of the use of this measure, but, if the child's condition is good, we can see no objection to it, and in some cases it is of definite advantage.

Single cases of rupture of the intestine in connection with attempts at reduction with contrast medium have been reported. It is obvious that when the intussusception is of such long standing that the intestinal wall is gangrenous such accidents may be possible. We have not encountered such ruptures, and the cases described in the literature (viz., a case of Nyborg's) in which the reduction enema caused a rupture of the intestine are not convincing with regard to the dangers of this procedure.

The age of our patients may also have influenced our results favorably. It is obvious that the pressure of the contrast medium is proportionately greater the younger the child, and the intestine of a young child is more responsive to the manipulation necessary in attempts at reduction.

SUMMARY

In 18 consecutive cases of acute intussusception during the first three years of life conservative treatment by means of an enema of roentgenologic contrast medium proved definitely successful.

Such favorable results seem to depend mainly on two factors: the short time elapsed before treatment (in most cases only a few hours) and the technic used in the administration of the reducing enemas of contrast medium.

ELECTROENCEPHALOGRAPHY OF THE NEWBORN

II. Studies on Normal, Full Term Infants While Awake and While Drowsy

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WHILE it is generally agreed that consistently reliable electroencephalograms are best obtained when persons are relaxed, at ease with their eyes closed and free from sensory stimulations, it is naturally quite difficult to obtain these ideal conditions in the study of infants. Since the potential importance of electroencephalography of the newborn infant has already been indicated,[1] it becomes necessary to establish normal patterns in various stages of alertness, so that electroencephalograms may be interpreted with some degree of confidence.

It is well known that the state of consciousness exerts a definite effect on the pattern of the brain waves.[2] For example, in the newborn period Smith[3] showed that the electrical activity noted over the sensory motor areas during sleep is abolished when the infant awakens. In the awake state the tracings are characterized chiefly by a flattened appearance..

In a previous communication[1] studies on the brain waves of normal, full term, sleeping infants in the newborn period were presented. It is the purpose of this paper to discuss our observations

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on the electroencephalographic tracings obtained from normal full term, newborn infants in various stages of alertness. The mothers of these infants had normal pregnancies, normal labors and deliveries and were delivered without the use of any analgesic or anesthesic agent. The babies all appeared clinically to be normal.

METHOD AND MATERIAL

Thirty-five electroencephalograms (EEG) were obtained on 25 newborn infants who ranged in age from 4 hours to 6 days. Several of these infants were studied on consecutive days to obtain longitudinal analyses.

The electroencephalographic technic employed and the type of machine used were described in a previous communication.[1]

Tracings were obtained on infants during three phases of consciousness: (1) while fully awake, (2) while drowsy and going to sleep and (3) when judged to be fast asleep. With the exception of those on babies only a few hours old, the electroencephalograms were obtained immediately after feedings. It was shown in a previous study [1] that when electroencephalographic runs were made on newborn infants immediately after feedings blood sugar levels were normal in more than 100 consecutive determinations. Therefore, in the present study blood sugar estimations were not performed. Naturally, it is conceivable that in the tracings obtained in the first hours of life, before feedings had been given, hypoglycemia might have influenced the character of the brain waves. However, the fact that tracings in the first hours did not differ noticeably from those obtained after feedings were started makes it unlikely that this was true.

RESULTS

Our results in the 25 newborn infants reported on in this study confirmed in part the observations of Smith [3] in regard to the electroencephalographic patterns characteristic of newborn infants while awake and while drowsy.

A. Wide-Awake Infants: 1. Monopolar Leads (fig. 1).—In contrast to the rhythmic activities noted in sleeping newborn infants reported on previously [1] the electroencephalogram of the wide-awake neonate is characterized by a decided flattening effect. Not only does rhythmic activity almost cease, but also there is practically no amplitude to the tracings, which appear as essentially straight lines with random fluctuations of low amplitude. While the tracings maintain an essentially flat, straight course, there are many periods in which they sway slightly to the extent of approximately 5 to 20 microvolts amplitude above and below the base line. We have been unable to determine any consistent rhythm to these small minor fluctuations. Certain portions of the tracings show almost none of them; other sections show them to occur at about 4 to 8 per second; still other sections show extremely minute saw-toothed fluctuations of not more than 5 microvolts amplitude superimposed on the small random waves.

The flattening effect mentioned previously as being characteristic of the electroencephalogram of wide-awake newborn infants was seen in only approximately half of the total lengths of the tracings. In the remaining half the tracings showed such conspicuous evidence of slight movements on the part of the infant that grossly irregular movement artefacts were present in long sections of the runs.

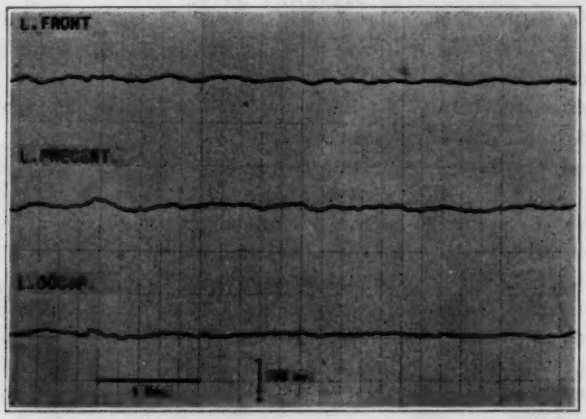

Fig. 1.—Monopolar leads in electroencephalogram of an infant 6½ hours old and awake. Note decided flattening effect in all leads. Several electrocardiographic artefacts are present.

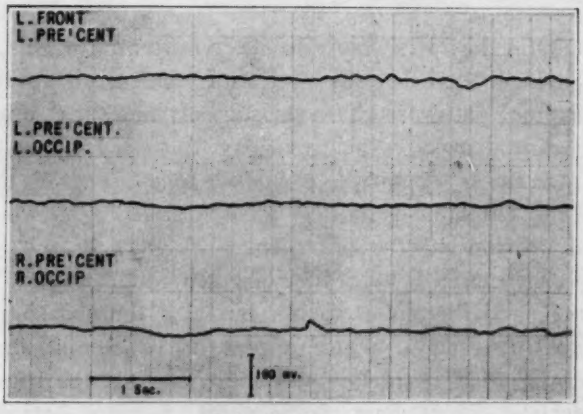

Fig. 2.—Bipolar leads in electroencephalogram of same infant as in figure 1. The infant was still awake. The character of the tracing is essentially the same as with monopolar leads.

2. *Bipolar Leads (fig. 2).*—All the remarks made in the previous paragraphs apply also to the bipolar tracings, which showed no discernible difference from the monopolar tracings.

B. Drowsy Infants: 1. Monopolar Leads (fig. 3).—As the infant progresses from an alert wide-awake state to a noticeably

drowsy condition, the chief characteristic of the electroencephalogram is the appearance in all leads of irregular random slow waves of increased amplitude with superimposed irregular minor fluctuations. The random waves vary widely in frequency, but, in the majority of tracings, they appear at the rate of 3 to 9 per ten seconds. The frequency of the minor fluctuations varies chiefly from 7 to 14 per second

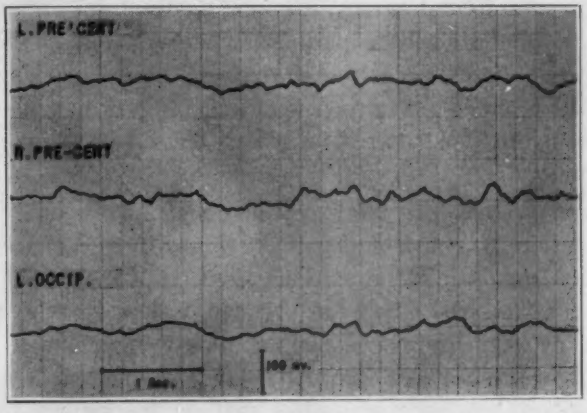

Fig. 3.—Monopolar leads in electroencephalogram of an infant 30 hours old and drowsy. Note increased activity in all leads. Several electrocardiographic artefacts are present.

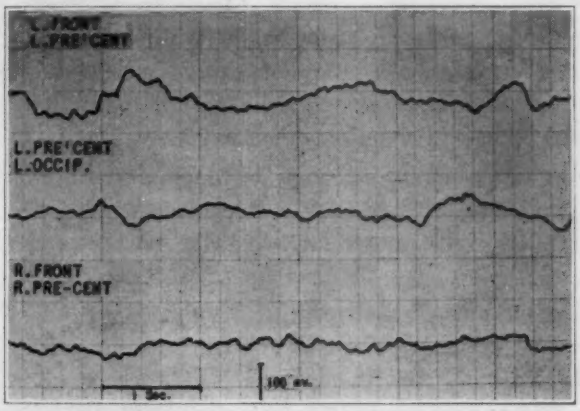

Fig. 4.—Bipolar leads in electroencephalogram of infant 13 hours old and drowsy. Activity is essentially like the monopolar tracing except for more base line sway in left frontal to left precentral lead.

and the amplitude ranges from 5 to 30 microvolts, with an occasional isolated wave going to 50 microvolts. The actual range of minor fluctuations was from 6 to 17 per second.

2. *Bipolar Leads (fig. 4).*—The "bipolar" tracings showed no discernible difference from the monopolar tracings taken in the drowsy state, except that the range of minor fluctuation was 5 to 16 per second.

C. Sleeping Infants.—The characteristics of the electroencephalogram in the normal, full term, sleeping infant were described previously.[1]

D. Effect of Leads.—There appeared to be no significant difference in the monopolar and bipolar tracings obtained from the frontal, precentral and occipital areas. We have observed no decrease in the amplitude of the frontal waves, as was reported for infants slightly older but out of the newborn period.[4] However, our electrodes were not placed over the extreme frontal areas of the brain. As mentioned before, we have noted that drowsiness and sleep bring out the amplitude of the electrical patterns, whereas the awake state results in their flattening.

E. Effect of Age.—In this study involving infants only in the first days of life there was no significant difference in the electroencephalographic patterns during the various days of the first week. For most of the infants the day by day tracings showed, with the exception of the artefacts of movement, an almost monotonous regularity, so that in selecting an electroencephalogram at random it was impossible to state at approximately what day the tracing was obtained.

SUMMARY AND CONCLUSIONS

Thirty-five electroencephalograms were obtained on 25 normal, full term, newborn infants born of mothers whose pregnancies, labors and deliveries were normal. The mothers received no analgesic or anesthesic agent during labor and delivery. Some of the babies were studied consecutively in the first days of life.

Monopolar and bipolar tracings were obtained from the frontal, precentral and occipital areas. Electroencephalograms were obtained in various states of alertness, including the awake state, drowsiness and sleep.

The characteristics of the tracings are described. The awake state exerts a decided flattening effect on the tracings. No differences were noted in the tracings from the various leads, and monopolar tracings showed no discernible differences from bipolar tracings. No significant changes in the pattern of the brain waves were noted from the first through the sixth day of life.

20 South Dunlap Street (3).

4. Lindsley, D. B.: Electrical Potentials of the Brain in Children and Adults, J. Gen. Psychol. **19**:285-306, 1938.

LACUNA SKULL AND CRANIOFENESTRIA

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J. N. BOET, M.D.
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DURING 1946 several children with craniofenestria associated with spina bifida were admitted to the pediatric clinic of the Binnengasthuis in Amsterdam, Netherlands. In association with Dr. G. A. Fehmers, we had the opportunity to study closely several cases of this anomaly.

Like several other investigators (Vogt and Wyatt,[1] Hartley and Burnett,[2] and Wieland [3]), we formed the opinion that this condition, though seldom recognized, is actually commoner than is generally thought.

In lacuna skull and craniofenestria (Lückenschädel), there are congenital bony defects in the skull. In lacuna skull these defects are restricted to the diploe and the inner table. No abnormality may be seen in the skull during life. Palpation reveals at the site of the defects a "springy" feeling, such as that in craniotabes (ping-pong-ball phenomenon). Post mortem, the lacunas show up clearly with transmitted light. They appear to be bordered with strong, bony ridges, which give the entire interior of the skull the appearance of a network (reticulated skull).

Craniofenestria is a true bony defect. On palpation the defective areas are clearly felt. The cranial contents may protrude through these defects, a condition called multiple encephaloceles; the surface, in consequence, becomes knobby. In addition to the defective diploe and inner table, the outer table is also absent; therefore, the dura is in contact with the periosteum. Again, the fenestrae are surrounded with bony ridges; the edges are studded with fine, bony lamellas, giving the appearance of filigree work.

From the Pediatric Clinic of the Municipal University of Amsterdam, Prof. Dr. S. van Creveld, Chief, and from the Pathologic Laboratory of the Binnengasthuis, Dr. R. van Dam, Chief.

1. Vogt, E. C., and Wyatt, G. M.: Radiology **36**:147, 1941.

2. (*a*) Hartley, J. B., and Burnett, C. W. F.: J. Obst. & Gynaec. Brit. Emp. **50**:1, 1943; (*b*) Arch. Dis. Childhood **18**:173, 1943.

3. Wieland, E.: Virchows Arch. f. path. Anat. **197**:167, 1909.

The sutures of the skull bones are often irregularly toothed. In both anomalies the defects are usually localized to the parietal bones and, according to Wieland,[3] are particularly common in the midline, but they also may be observed in the frontal or occipital bone, in the alae magnae of the sphenoid bone and in the squamous portion of the temporal bone. They vary in size, shape and number. They are not usually symmetric. Other bones of the skull and its base are normal in structure.

Lacuna skull and craniofenestria may be difficult to distinguish from each other, and intermediate forms occur. They are often seen with spina bifida; the form of craniofenestria associated with herniation is usually combined with a myelomeningocele. The localization of the spina bifida has no influence on the more or less pronounced character of the anomaly. According to Vogt and Wyatt,[1] the majority, about 91 per cent, of the meningoceles lie in the thoracic portion of the spine.

In addition to these anomalies of the spinal column and spinal cord, the following malformations are also reported: cleft palate, deformities of the ribs,[4] clubfoot (as in our second case [5]), bony defects of the humerus, absence of the radius [5] and congenital cardiac anomalies.[4] The general appearance of the bony skeleton is often unusual: senile features, slanting eyes, sunken bridge of the nose, broad zygoma and prognathism.[6] Hydrocephalus is often present, but microcephaly and normal skeletal form are also reported.

The incidence has been reported to be higher than one would expect. Vogt and Wyatt,[1] who made no distinction between lacuna skull and craniofenestria, reported an incidence of 43 per cent of 120 newborn infants with meningoceles. In 5,000 newborn infants without meningoceles, the incidence appeared to be only 0.04 per cent. According to Hartley and Burnett,[2] cranial lacunas occur in 0.8 per cent of all the newborn. They advise roentgenographic examination before birth in cases of polyhydramnios and hydrocephalus, conditions in which craniofenestria may be expected.

That the cranial lacunas are seldom diagnosed is, in our opinion, partially due to the fact that no characteristic abnormalities need be present. Therefore, one has usually no incentive to make roentgenograms of the skull. Lacuna skull or craniofenestria should be thought of in all cases of spina bifida, as well as in those of hydrocephalus and abnormalities of facial appearance, such as mongolism and others

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4. Rothbart, H. B.: Lacunar Skull of New-Born, Am. J. Dis. Child. **52**:1375 (Dec.) 1936.

5. von Recklinghausen, F.: Virchows Arch. f. path. Anat. **105**:243, 1886.

6. Faust, H.: Beitr. z. path. Anat. u. z. allg. Path. **86**:613, 1931.

revealing characteristics previously described. In roentgenograms the flat bones of the skull appear thin, and, compared with those of normal children, they ossify late (Van Leeuwen [7]). The sutures and fontanels may be wider than normal. The most characteristic sign is the multiple areas of diminished density bounded by bony ridges. The boundary in craniofenestria is sharper and the contrast in structure more pronounced than in lacuna skull.

Hartley and Burnett [2] stated that a definite diagnosis can be made only from a lateral roentgenogram. Inspection of the parietal areas is most important, as the occipital and frontal regions may normally present an appearance confusingly similar. The presence of herniation on the roentgenogram is an argument in favor of the presence of fenestrae as opposed to lacunas.

The progress of the conditions accompanying lacuna skull and craniofenestria depends largely on whether or not the defects are associated with a meningocele. If they are, death due to progressive hydrocephalus or meningitis is usual. In a few children with lacuna skull without other abnormalities, the lacunas tend to disappear slowly, but remnants will probably always be seen on roentgenogram. Dorrance [8] reported the case of a youth 17 years of age who had craniofenestria without spina bifida that showed no tendency to heal. Two similar cases were described by Weill-Hallé and Weill.[9]

In differential diagnosis the following facts must be considered:

1. In the normal child frontal and posterolateral fontanels should close rapidly.
2. Symmetric parietal fenestrae, a hereditary and familial condition of the parietal bones, described by Halbertsma [10] and others, may be present. Some investigators do not distinguish this condition from craniofenestria. In our opinion, such a distinction should be made.
3. Cranium bifidum, a defect involving the sagittal sutures, is also frequently associated with spina bifida.
4. Lacuna skull and craniofenestria are not associated with any disorders in calcification of the other bones, and no abnormalities in blood chemistry occur, as in rickets. Histologically, there are other differences (Wieland [3]) with rickets.

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7. Van Leeuwen, K.: J. Pediat. **28**:193, 1946.

8. Dorrance, T. O.: Lacuna Skull (Lückenschädel), Am. J. Dis. Child. **60**:359 (Aug.) 1940.

9. Weill-Hallé, M. M. B., and Weill, J.: Bull. Soc. de pédiat. de Paris **26**:497, 1928.

10. Halbertsma, T.: Maandschr. v. kindergeneesk. **9**:89, 1940.

5. Congenital syphilis, fragilitas ossium, reticuloendothelioses and osteopetrosis can all result in skeletal defects, but each affects the entire skeleton and does not raise diagnostic difficulties. The same holds true for leukemia (blood picture diagnostic) and cleidocranial dysostosis (disturbance in development of the clavicles).
6. Pressure lacunas of the skull (de Lange [11]), a condition which is not congenital, and craniostenosis, in which the sutures close abnormally early, may simulate craniofenestria and are often confused with it. In neither condition are the characteristic bony ridges around the lacunas present.

The theories assumed to explain craniofenestria and lacuna skull fall into three groups. First, the theory of increased intracranial pressure during intrauterine life.[12] The craniofenestria is said to be due to the fact that in the later months of gestation the cranial contents grow faster than the skull. Craniofenestria with herniation, which occurs only with spina bifida, is taken to be a result of the abnormal pressure extended by internal hydrocephalus. The pathologic pressure increases and enlarges the defects by the pressure of growth.[3]

Sicher [13] claimed that the meningeal vessels, which run over the ridges, were interrupted, owing in her opinion, to intracranial pressure. She observed no thickening of the intima, as described by Erdheim.[14]

Some authors considered cerebral pressure due to occipitoposterior presentations of importance; actually, craniofenestria is also observed in instances of breech presentation [15] and in those of transverse presentation, as in 1 of our cases.

A disturbed balance between the pressure of the amniotic fluid and intracranial pressure was also considered.[16] This disturbance is thought to occur by virtue of the flow of the cerebrospinal fluid out through the meningocele, bringing the cerebral contents in direct contact with the bones. The growth pressure (which is greater than normal) then causes atrophy of bone. Increased intracranial pressure is not essential, but it can enlarge the defects. The defects and impressions can begin only in intrauterine life, for after birth the counterpressure of the amniotic fluid disappears and the skull can enlarge.[12b]

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11. de Lange, C.: Ann. pædiat. **158**:97, 1942.
12. (*a*) West, J. F.: Lancet **2**:552, 1875. (*b*) Kerr, H. D.: Am. J. Roentgenol. **30**:458, 1933. (*c*) Faust.[6]
13. Sicher, L.: Frankfurt. Ztschr. f. Path. **25**:497, 1921.
14. Erdheim, J., cited by Sicher.[13]
15. Abels, H.: Klin. Wchnschr. **6**:2040, 1927.
16. Folkerts, J. F.: Spina bifida, diplomyelie en enuresis nocturna, Thesis, Amsterdam, N. V. Noord-Hollandsche Uitgevers Maatsch., 1946.

The second theory suggests a disorder of development. Von Recklinghausen [5] pointed out the association of spina bifida and defects of the skull and claimed that they both depended on a developmental abnormality. Thoma [17] and Cohn [18] looked on craniofenestria as a congenital hypostosis. Hartley and Burnett [2] rejected the theory of retarded development, as the ridges are thicker than in the normal skeleton of the newborn, and they looked on the condition as a developmental disturbance in which two processes may be associated, i. e., absence of ossification of the membranous skull bones and absence of chondrification of the vertebral arches. They doubted whether the association could be genetically determined. Investigation concerning inheritance had little result.

Some authors proposed a combination of a primary disturbance in development of the skull bones and elevated intracranial pressure.[4]

According to a third theory, craniofenestria is a result of other diseases, rickets being a frequently mentioned cause. Wieland [3] was able to exclude this possibility on histologic grounds. Syphilis cannot be considered an etiologic factor, as it is roentgenologically and histologically different.

REPORT OF CASES

Case 1.—M. B., a girl born March 9, 1946, was admitted on March 11 to the pediatric clinic at the Binnengasthuis, Amsterdam. She was a full term child; the weight at birth was 3,800 Gm. The parents and family were healthy. Labor was normal, but during the first three months of pregnancy the mother had vomited frequently and had lost much weight. The mother's nutrition during that time left much to be desired; she received few potatoes and vegetables, no fruit or extra vitamins and little fat, with barely 100 Gm. of milk and 25 Gm. of meat.

The child had a large lumbar meningocele, with paresis of both legs. A large portion of the bony cranium was absent, and the contents protruded. The defects were bordered with strong bony ridges. The remainder of the cranium was thin and showed the ping-pong-ball sign. The features were normal, and the thoracic and abdominal contents showed no abnormalities. Reflexes in the legs were absent, but other reflexes, including the labyrinthine reflexes, were normal (Prof. De Kleyn). Studies of the blood and urine showed no abnormalities.

Roentgenographic Studies.—Poor calcification of the bones, wide sutures and numerous small and large holes, bordered with thick bony ridges (fig. 1) were revealed. Protrusions beyond the cranial outline were clearly visible.

The child died of meningitis on March 26.

At postmortem examination no macroscopic or microscopic abnormalities were observed in the thoracic or abdominal organs. Spina bifida of the lumbosacral region was present, but unfortunately, it was not determined whether a meningocele or myelomeningocele was present. When the scalp had been removed, the herniations could be clearly seen. They were most pronounced in the parietal bones near

17. Thoma, R.: Virchows Arch. f. path. Anat. **212**:1, 1913.
18. Cohn, M.: Jahrb. f. Kinderh. **106**:333, 1924.

the sagittal sutures. The protrusions were covered with a transparent membrane containing patchy plaques of bone (fig. 2). One obtained the impression that the cerebral contents lay immediately below. The fontanels and sutures were wide.

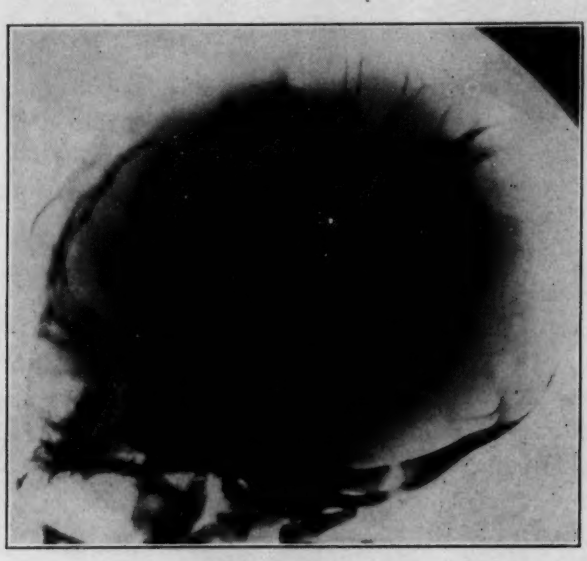

Fig. 1.—Roentgenogram of head of M. B. (case 1), showing large and small fenestrations, surrounded by thick, calcified ridges.

Fig. 2.—Photograph of M. B. (case 1), showing skull after removal of scalp; defects are clearly seen as well as protrusion of contents of the skull.

There was no perforation. The frontal and occipital bones also showed protrusions. On the interior of the skull bones, ridges surrounding the thinned areas and defects (figs. 3 and 4) were visible. In the membranous defects fairly large dural vessels were present, which were clearly visible after removal of the scalp. The cerebral

gyri were slightly flattened and the sulci shallow. After fixation, certain groups of gyri appeared to fit into impressions in the cranium. The lateral ventricles and third ventricle, as well as the foramen of Monro, were large. The septum pellucidum was partly absent, and the corpus callosum was smaller than normal. The cerebellum was noticeably small and had small gyri. Histologically, these gyri appeared to have a broad external granular layer.

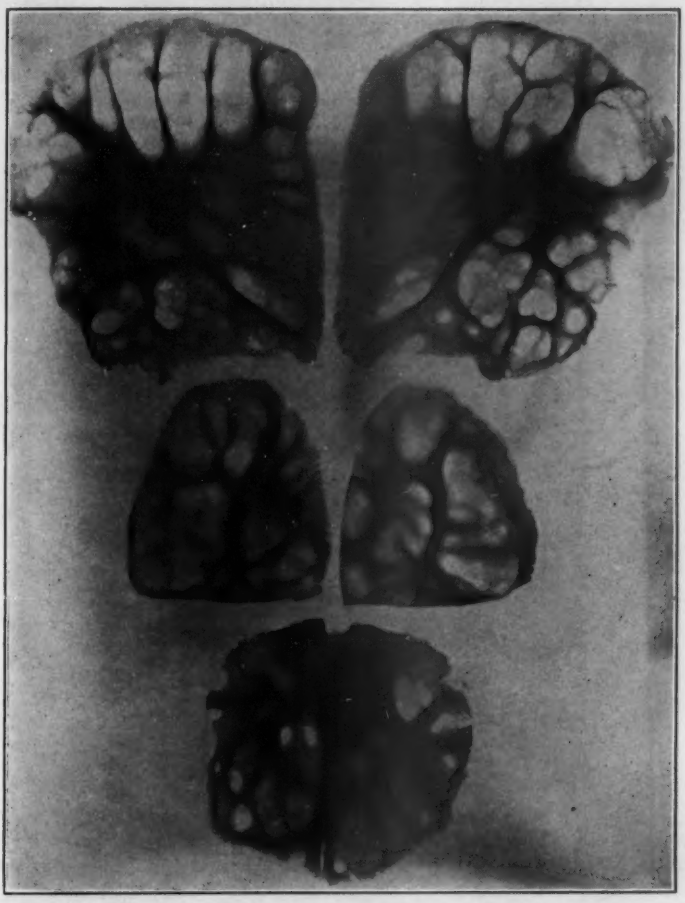

Fig. 3.—Roentgenogram of individual bones of the skull of M. B. (case 1).

Between the pial vessels we observed clumps of mononuclear cells, with a few polymorphonuclear inflammatory cells. At the base of the brain, at the level of the corpora quadrigemina, were signs of purulent meningitis. The aqueduct was open and of normal size. A section from the edge of the parietal bone showed underdeveloped structure, the bone being in a very primitive stage. On the dural aspect little osteoclasis was visible; in some areas there was even formation of new bone. The outer table was decidedly underdeveloped for the age. Here and there a bony lamella was visible. In the membranous defect, as in the connective tissue between the bony lamellas of the outer table, a tendency to formation of new bone was visible.

CASE 2.—M. M., a girl born May 14, 1946, was admitted on May 25 to the Binnengasthuis because of spina bifida. Labor had been normal; weight at birth was 3,300 Gm. The mother had vomited daily in the first three months of pregnancy. In this case nutrition had been provided by the official ration, which in the summer of 1945 could still be called deficient. The parents and a brother of the patient were normal. The mother's two brothers had had nocturnal enuresis until the age of 12, but neither showed spina bifida occulta on examination.

The child did not appear ill. She was mongoloid in appearance. There were no visible signs on the scalp; the circumference of the cranium was 34 cm. The fissures were wide, and behind both ears weak spots in the bones were felt. The left parietal bone had a defect of 1 cm. in diameter. The fundi (Dr. Roelofs) were

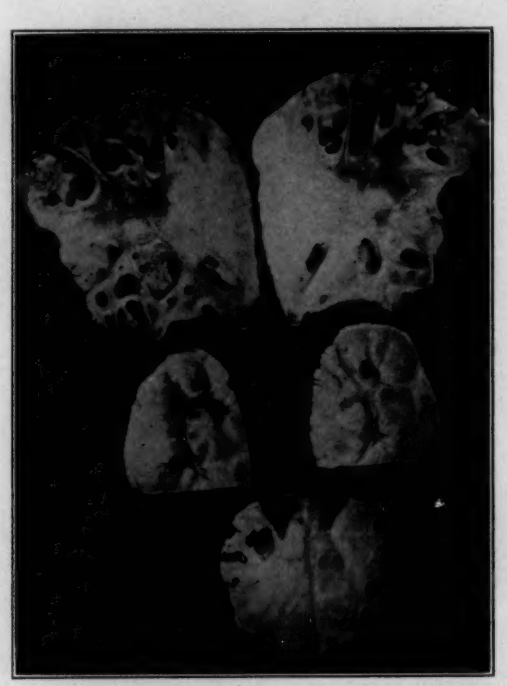

Fig. 4.—Cleared bones from the skull of M. B. (case 1). The filigree-like structure is clearly shown in the left parietal bone; edges of the bones are toothed and ridges are perpendicular.

normal, as were the thoracic and abdominal contents. The left leg was weak and had a clubfoot. The reflexes could not be elicited, and there was limitation of movement in the left knee. The muscular tone of the right leg was diminished. A large meningocele extended from the first lumbar to the second sacral vertebra. On roentgenograms the bodies of the fourth and fifth lumbar vertebrae appeared to have coalesced.

No evidence of rickets was seen in the bones. A roentgenogram of the skull showed protrusions. Clear defects in the parietal bones were visible. The sutures and fontanels were wide. The cranial bones were poorly calcified.

The urine, the labyrinthine reflexes and the blood count were normal. The Wassermann reaction of the blood was negative. Measurements of calcium and alkaline phosphatase in the blood gave normal values. The amount of inorganic

phosphorus did not exceed 3.4 mg. per hundred cubic centimeters on repeated examinations, not even after stimulation with 500,000 units of vitamin D. In the next eight weeks the cranial circumference increased by 3 cm. The child died on July 18 from cachexia due to meningitis. Permission to perform a postmortem examination was refused.

The following 3 patients were seen at the pediatric department of the Onze Lieve Vrouwe Gasthuis (Dr. G. A. Fehmers).

CASE 3.—J. H., a boy born July 7, 1946, was admitted on the same day to the Onze Lieve Vrouwe Gasthuis, Amsterdam, with spina bifida. He was a full term child, weighing 3,430 Gm.; birth had been normal, without cyanosis or asphyxia. The parents and relatives were normal. The mother had had influenza in the sixth month of pregnancy. The child did not appear dull; he whimpered now and then. Examination revealed that he was slightly edematous. The head was large (circumference, 40 cm.), and the fontanels were wide and protuberant. On palpation several defects were suspected. No nuchal rigidity was present. The facies were normal except for convergent strabismus. The thoracic and abdominal organs were normal. There was a spina bifida from the eleventh thoracic to the fourth lumbar vertebra, with a meningocele the size of a mandarin. The right leg showed flaccid paralysis; the reflexes were absent, and sensation was disturbed. Abdominal reflexes were absent, except in the right upper quadrant. The anal reflex was present, but the cremasteric was absent.

On July 11 the left leg showed flaccid paralysis. Roentgenograms of the skull showed typical craniofenestria, with a network of ridges and wide sutures. A roentgenogram of the spine revealed "hour-glass" lumbar vertebrae. The third and fourth lumbar vertebrae were coalesced. A questionable fissure of the pelvis was seen. The other bones were normal. On July 11 convulsions supervened, and the child died. Permission for postmortem examination was refused.

CASE 4.—T. T., a girl born June 16, 1946, was admitted to Onze Lieve Vrouwe Gasthuis for spina bifida on June 17. The parents and relatives were in good health. Delivery was with version and extraction, owing to transverse presentation. She was a full term child, weighing 2,650 Gm. with a mongoloid appearance; the bridge of the nose was wide and sunken. Slight prognathism was evident. The cranial circumference was 35 cm.; the fontanels were wide and tense, and clear defects were palpable in the left parietal and occipital bones. Internal organs showed no abnormalities, but spina bifida and meningocele were present from the eighth thoracic vertebra to the fourth lumbar vertebra. Both legs were paretic, and there was equinovarus of the right foot. Reflexes in both legs were absent. The blood count was normal.

A roentgenogram of the skull showed poorly calcified bones, with clear fenestration and large unossified areas, surrounded with thickened ridges (fig. 5). A roentgenogram of the spine showed an untidy picture of partial coalescence of the hemivertebrae from the seventh thoracic to the third lumbar vertebra. The child died on July 24 with signs of bronchopneumonia.

At autopsy a patent foramen ovale was observed. Widespread bronchopneumonia of the lower lobes of both lungs was evident. The remaining internal organs were normal.

The dura was densely adherent to the cranium. The interior of the left parietal bone showed ridges radiating from the center of ossification. Between these ridges were indentations. Two membranous defects were seen on the posterosuperior aspect of the bone. The ridges were less obvious on the right parietal bone, and

only one membranous defect was present near the occipital bone. The frontal and occipital bones also showed ridges with intervening depressions, into which groups of gyri fitted. Large vessels ran over the ridges, but in the defects smaller vessels were also seen.

The brain weighed 630 Gm. The convolutions were broad and flattened and the sulci shallow. On section the ventricles were seen to be large. The foramen of Monro was increased in size, but the aqueduct was normal. The cerebellum and medulla were normal. The meninges showed an inflammatory reaction on section, but sections of cerebral and cerebellar origin showed no abnormalities.

Histologically, the bony ridges were built up of small lamellas with intervening marrow spaces. On the dural side the lamellas were broader and better calcified than on the periosteal side, and in the latter site there was clear evidence of bone

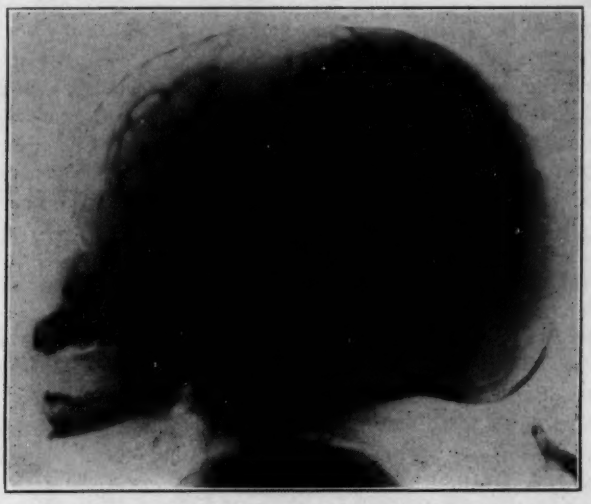

Fig. 5.—Roentgenogram of head of T. T. (case 4). Clear bony ridges with lacunas and fenestrations are evident.

formation. The outer table was absent. In the membranous defects, in the center, as well as at the edges, there were signs of intramembranous ossification, with a tendency to closure of the defects (figs. 6 and 7).

CASE 5.—A. D., a boy born Jan. 14, 1947, of healthy, but poor, parents, was admitted to Onze Lieve Vrouwe Gasthuis, Amsterdam, on January 16 with a spina bifida. The first child in the family had also had a spina bifida; the succeeding 3 children were normal. Pregnancy and labor had been normal. The weight at birth was 2,950 Gm. The child had a mongoloid appearance; the bridge of his nose was broad and sunken, and prognathism was obvious. The cranial circumference was 36 cm., the sutures were wide, and the forehead presented an encephalocele. On the left and right parietal bones several defects of varying size were palpable; they were not symmetrically distributed. The skull felt lumpy. At the level of the lumbosacral area was a large meningocele the size of a mandarin. There was bilateral spasticity of the legs and bilateral clubfoot. No abnormalities in the internal organs were apparent.

Roentgenograms of the skull showed numerous sharply outlined defects, surrounded by strong, calcified ridges, varying in diameter from 1 to 3 cm.

Roentgenograms of the spine and pelvis revealed bilateral dislocation of the hip and a meningocele in the lumbar portion of the spine. No further skeletal abnormalities were seen. The blood picture was normal. During the next fourteen days the cranial circumference increased by several centimeters, and the child died on January 30 with symptoms of meningitis.

Postmortem examination (Dr. H. M. van der Linde) revealed that the lumbar myelomeningocele was filled with pus. No abnormalities were detected in the

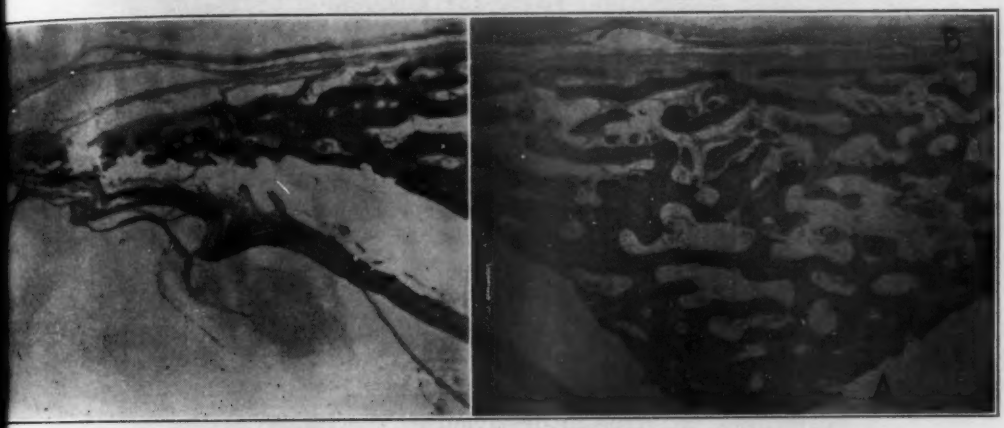

Fig. 6.—Photomicrograph of a lamella from T. T. (case 4): *A* indicates dural side; *B*, the periosteal side, and *C*, the membranous defect with ossification.

Fig. 7.—Photomicrograph of the parietal bone from a normal newborn infant of the same age as T. T. (case 4). The external and internal table are already present. The difference from the appearance of figure 6 is obvious.

internal organs except for a patent ductus Botalli in the lumen band large enough to admit a quill (3 mm.).

No abnormalities of the soft scalp were observed. Sutures and fontanels were wide. The dura was adherent to the skull. The internal surface of parietal bones showed thick ridges radiating out superiorly and occipitally from the center of

ossification. Between the ridges, thinned areas and round and oval defects were visible. The cranial contents protruded through them. The changes were most pronounced in the parietal bones, but on the frontal and occipital bones ridges and depressions, but no actual defects, occurred. Most of the vessels ran over or under the ridges, while a few crossed a depression. The defects were not without vessels. Groups of gyri fitted into the depressions. The cerebrospinal fluid was turbid, and over the left hemisphere and at the base of the brain there was pus. The gyri were flattened and the sulci shallow. The cerebral and cerebellar gyri were normal. The lateral ventricles appeared slightly enlarged, but not so much as in cases 1 and 2. The meninges over the cerebrum and cerebellum showed histologic evidence of inflammatory infiltration. The cerebellum still showed a fairly wide external granular layer. No inflammatory reaction was seen in the cerebrum.

The bony ridges appeared to be built up of lamellas with intervening marrow spaces. The subperiosteal lamellas were in the second stage of ossification and those in the deeper layers in the third stage. The outer table could be seen, but it had many defects. In the defective areas there was a tendency to formation of bone, and this tendency was also noticeable on the edges of the membranous defects and in the formed bony tissues.

COMMENT

When we consider our observations in the light of the aforementioned theories, we come to the following conclusions:

1. Although in all our cases a definite internal hydrocephalus was present and although the bony ridges fitted into the sulci, we could find no evidence that increased intracranial pressure was the main cause. There was no parallelism between the degree of bony change and the intracranial pressure. In our fourth case hydrocephalus was present, but the bony changes were least conspicuous. No evidence of resorption was present in formed bone, such as would be expected in pressure atrophy. The possibility that the blood supply suffered through pressure we could exclude. Lastly, if increased cerebral pressure were an important factor, we should expect craniofenestria to be commoner in conditions with an increased intracranial pressure, conditions in which the bony container of the skull and spinal column is closed and in which such compensation as is given by spina bifida, as in our cases, is absent.

2. The fact that craniofenestria is constantly associated with spina bifida indicates a developmental disorder. Study of the literature shows that the brain has not been adequately studied. Only Rothbart[4] reported histologic studies of the brain. In his cases there appeared to be a developmental disturbance of the cerebellum as well. This disturbance could mean that the defects of the skull might be connected with the condition of the central nervous system in the same way as spina bifida is with the spinal cord. Craniofenestria and spina bifida would then be similar developmental disorders.

In 3 cases autopsy revealed a fairly wide external granular layer in the cerebellum, a condition which cannot be considered actually pathologic at this age. In 1 of our cases there was clear hypoplasia of the cerebellum. Other than these malformations, no developmental anomalies were observed.

3. The defective development of the inner table and the appearance of strong bony ridges suggest a disturbance in ossification. In addition to the developmental disorder, we wish to consider another suggested factor. Five cases of craniofenestria were seen in two clinics in Amsterdam; 4 were seen within four months in children conceived shortly after World War II. So far as we know, no mention of the condition is to be found in the Netherlands literature prior to the war. In experimental work, Warkany and Nelson [19] successfully produced several congenital defects, including cranial defects, in the progeny of female rats fed a deficient diet during pregnancy. In our cases it is also possible that the deficient diet of the mother was an etiologic factor, in view of the poor nutritional conditions in the Netherlands during recent years. Schachter [20] also mentioned the fact that Hartley and Burnett's patients all belonged to the poorer classes, an observation which is also true of our patients. In addition, 2 of our mothers had had hyperemesis gravidarum. Extra rations for pregnant women in Netherlands were granted only in the latter months of their pregnancy, when the deficiency of the maternal diet probably had already exerted its influence on the organogenesis.

SUMMARY

Clinical and pathologic observations on several cases of craniofenestria seen within a few months in 1946 in Amsterdam, Netherlands, are reported.

Emphasis is laid on our impression that this condition is caused by a developmental disturbance, which perhaps is due to malnutrition of the mother during pregnancy.

19. Warkany, J., and Nelson, N. C.: Am. J. Roentgenol. **47**:889, 1942.
20. Schachter, M.: Ars med. **2**:124, 1947.

NEPHROSIS IN CHILDREN

I. Observations on Eighty-Four Patients

II. Clearance and Saturation Tests

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I. OBSERVATIONS ON EIGHTY-FOUR PATIENTS

IN THE last ten years a total of 84 patients with nephrosis have been studied at the Children's Hospital, Habana, Cuba. They were classified according to a clinical picture of more or less generalized pitting and recurrent edema, oliguria, albuminuria, hypoproteinemia, hypercholesteremia and high incidence of bacterial infection.

Nephrosis is a common disease of early childhood. The majority of patients observed were 2 to 4 years of age, and the youngest was 10 months old. White children definitely predominated, with only a few Negro patients. Slight predominance of boys was also seen (fig. 1).

Nephritic symptoms, such as hematuria, hypertension and urea retention, were seen as a group or independently in 83 per cent of patients. In 8 children the onset and subsequent course of illness were without nephritic symptoms. Hematuria, as evaluated by the Addis count of urinary sediment,[1] was observed in 79.7 per cent of nephrotic children (fig. 2). Of these children, 60 per cent showed abnormal numbers of red blood cells in the urine from the beginning of illness. Hematuria was observed to be an early or late, persistent, transient or recurrent symptom in the evolution of the nephrotic syndrome. Some patients having initial hematuria showed a subsequent course of "pure lipid nephrosis" and vice versa. A close relation could not always be established between intensity of hematuria and extension of glomerular involvement. The absence of hematuria did not exclude the possibility of inflammatory changes in the kidneys of nephrotic children.

Urea retention in the blood in amounts above 35 mg. per hundred cubic centimeters was reported in 61.9 per cent of patients, and blood pressure at higher than standard figures for the various ages was

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This paper was read at the First Pan-American Pediatric Congress, Washington, D. C., July 7, 1947, and at the meeting of the Chicago Pediatric Society, July 28, 1947.

1. Galán Conesa, E.: Nefropatías del niño: Estudio del sedimento urinario por el método de Addis, Bol. Soc. cubana de pediat. **14**:387 (Aug.) 1942.

observed in 44 per cent of patients. Dilatation of heart (seen on orthodiagram) and myocardial damage (detected by electrocardiogram) were recorded for 14.2 and 4.8 per cent, respectively. Frequency of other symptoms is shown in table 1.

In contrast to high incidence of nephritic symptoms in nephrosis, only 4 patients showed the clinical picture of chronic glomerulonephritis. In a girl renal rickets and hypertension developed, and she died from heart failure seven years after the onset of her illness. The first hematuria was observed after two years of illness. The illness in a second child ran the course of "stormy nephritis," and at autopsy typical crescent fibrosis of the glomerular capsule was observed. A third child died from pneumonia, but autopsy revealed enlargement of the kidneys, with adherent capsule, grayish discoloration and granular appearance

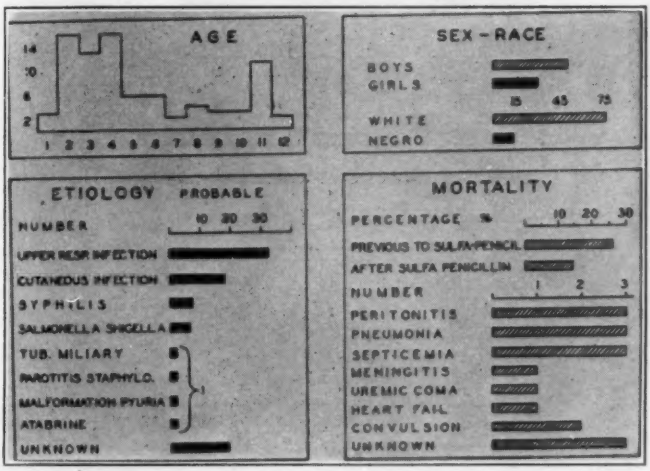

Fig. 1.—Graphs showing data gathered from observations on 84 cases of nephrosis.

of the surface. Hematuria in this patient was never above 13,000,000 red blood cells per twelve hours, and specific gravity was 1.021 a few days before death.[2] In a fourth child permission for postmortem examination was not given, but she had a nonhematuric nephrotic syndrome for four years. During the last eight months of illness, progressive azotemia (up to 200 mg. per hundred cubic centimeters) and retention of creatinine (up to 7.5 mg. per hundred cubic centimeters) were observed. Blood pressure reached as high as 180 systolic and 120 diastolic. The roentgenologic clearance of iodopyracet showed a serious impairment of renal function. A severe renal acidosis (carbon dioxide–combining power of 10 volumes per cent) was controlled with sodium

2. Galán, E.: El síndrome nefrosico en el niño: Observaciones sobre 43 casos, Arch. Soc. estud. clín. Habana **38**:445 (May-June) 1944.

lactate solution, but she became more edematous and died suddenly one week later at the age of 6 years.

It remains to be seen how many of these children surviving severe bacterial infection will show a subsequent course of chronic glomerulonephritis.

Inflammatory and/or proliferative changes were observed in all but 1 patient of 10 on whom autopsies were performed and 3 for whom biopsies on specimens of kidney were made. These changes were greatly dependent on three important factors: predominance of nephritic symptoms at the onset and during the clinical course, activity and type of intercurrent or focal bacterial infection and duration of illness. Mod-

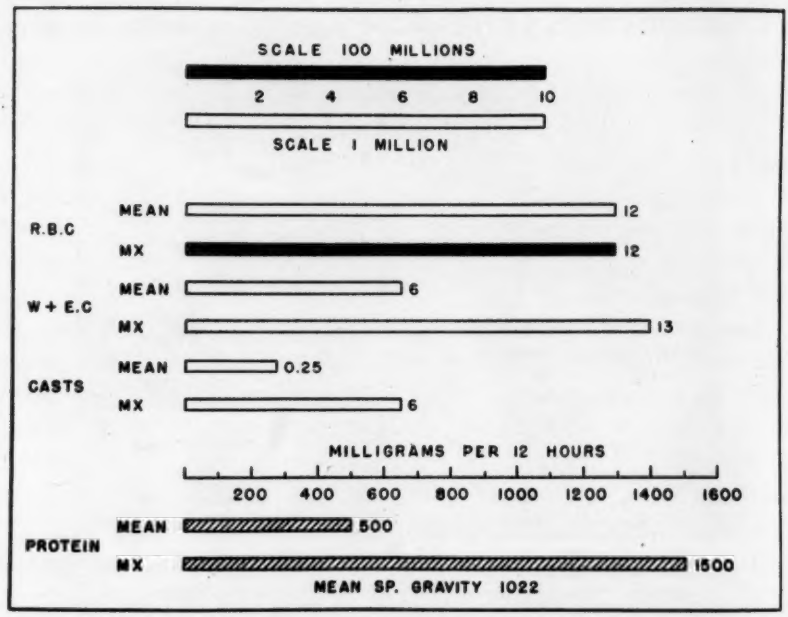

Fig. 2.—Graph showing results of the Addis count in 72 children with nephrosis. The upper portion shows mean and maximum values for red blood cells, white and epithelial cells and casts, respectively, while the lower part shows mean and maximum values for protein in milligrams per twelve hours.

erate focal inflammatory changes in glomeruli and interstitial connective tissue were usually observed in cases of early death from bacterial infection. Advanced cases, on the other hand, showed more or less extensive inflammatory and proliferative lesions involving glomerular structures, interstitial connective tissue and the vascular system. Atrophy of tubular epithelium was usually associated with obliteration of glomerular tufts. Thickening of basement membrane, as pointed out by Bell,[3] was also seen in some cases (fig. 3). A biopsy specimen of

3. Bell, T.: Renal Diseases, Philadelphia, Lea & Febiger, 1946, pp. 198-220.

kidney taken at the end of the second year of illness from a child having neither hematuria nor hypertension but with low values for clearance and saturation tests showed areas of interstitial nephritis, with obliteration of small arterioles and crescent formation in a few glomeruli (fig. 4). On the other hand, the infant who did not show glomerular lesions at postmortem examination had as many as 30,000,000 red blood cells in the urine and died from miliary tuberculosis.[2] Associated conditions were seen in 3 cases. Splenomegalic cirrhosis of the liver with "spider web" telangiectasis and final hematemesis characterized a typical case of nephrosis. Hypothyroidism, diabetes mellitus and great enlargement of

TABLE 1.—*Frequency of Symptoms of Nephrosis in 84 Patients*

Symptoms	No. of Patients	Per Cent	Symptoms	No. of Patients	Per Cent
Edema	84	100	Bacterial infection	66	78.5
Oliguria	84	100	Increased sedimentation rate	80	95.2
Hypoproteinemia	84	100	Fever	66	78.5
Hyperlipemia	84	100	Leukocytosis	57	67.8
Albuminuria	80	95.2	Polynucleosis	52	61.9
Casts in urine	65	77.3	Abdominal pain	29	34.7
Hematuria (Addis count)	67	79.7	Nonspecific diarrhea	20	23.8
Blood pressure above normal	47	44.0	Anemia	12	14.2
Urea retention (above 35 mg./100 cc.)	52	61.9	Hepatomegaly	16	19.0
Dilatation of heart (orthodiagram)	12	14.2	Splenomegaly	2	2.3
Myocardial damage (electrocardiogram)	4	4.8	Convulsions	4	4.7
Heart failure (cause of death)	1	1.2	Uremic coma	2	2.3
Retinitis (with exudate)	1	1.2	Low basal metabolic rate (39 determinations)	11	28.2
Renal rickets	1	1.2	Associated conditions		
Renal diabetes	1	1.2	Cirrhosis of liver	1	1.2
			Hypothyroidism and diabetes mellitus	1	1.2
			Arrest of ossification centers	1	1.2

Results of Laboratory Studies

Determinations	Total No. Determinations	Mean Value	Maximal Value	Minimal Value
Total plasma protein, Gm./100 cc.	229	4.76	6.78	2.18
Plasma albumin, Gm./100 cc.	163	2.61	4.62	1.00
Plasma globulin, Gm./100 cc.	163	2.35	3.95	1.04
Cholesterol, mg./100 cc.	225	424	880	177
Urea, mg./100 cc.	185	57.60	180.00	21.00
Sedimentation rate (Westergren), mm./min.	80	109	175	25

spleen were seen in a boy, a biopsy specimen of whose kidney showed widespread interstitial nephritis. The third patient had arrested ossification centers without thyroid deficiency, but examination showed 150,000,000 red blood cells in the urinary sediment. Thyroid therapy did not change the roentgenologic appearance of ossification centers but raised the basal metabolic rate from —20 to +35 per cent.[2]

Investigations conducted in regard to the influence of extrarenal factors on the pathogenesis of nephrosis all showed negative results. Enlargement of the liver was transitorily observed in 19 per cent of patients, but no strong clinical, functional or pathologic evidence was seen suggesting the participation of this organ, nor were the thyroid gland, reticuloendothelial system or hypothalamus involved in the pathogenesis of the disease. Aspiration biopsy specimens of liver and

results of hepatic function tests were normal. In contrast to lack of evidence favoring extrarenal factors, involvement of kidneys in every patient was demonstrated by repeated Addis counts of urinary sediment, clearance and saturation tests, biopsies and postmortem examinations.[3]

Bacterial infection was the most probable cause of nephrosis and its nephritic episodes. Most patients had a history of infection almost immediately before the development of edema. Though many investigators favor an obscure etiologic basis, I feel that the majority of cases of the disease in children are closely related to bacterial infection. Cutaneous infection (impetigo and pyodermitis) is the second leading

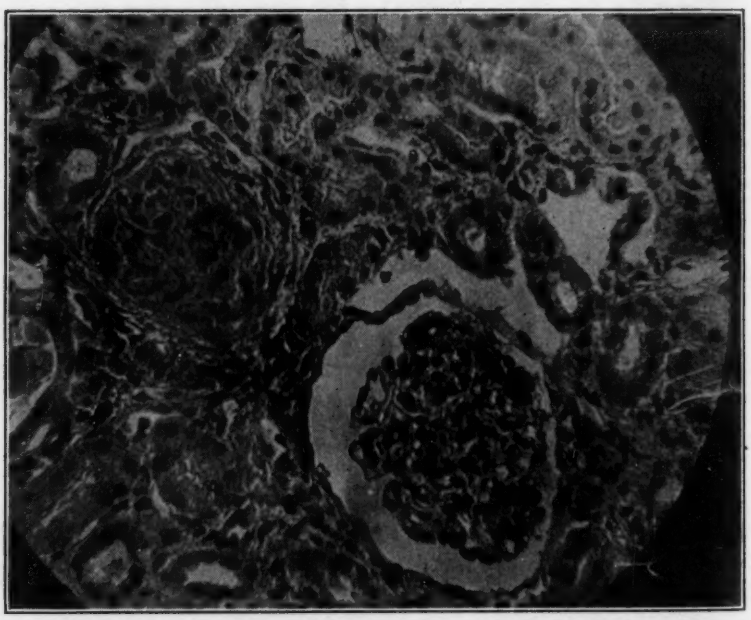

Fig. 3.—Photomicrographs of biopsy specimen from kidney of patient R. F. who had neither hematuria nor hypertension, but whose values for clearance and saturation tests were low. Total obliteration of glomerular tuft (upper left) and increased cellularity of glomerulus (lower right) are apparent.

cause of children's nephropathies in Cuba. This same criterion was supported by Baeza-Goñi [4] for Chile. Cause and effect relationship is easy to determine in children with cutaneous infection, not only for acute hemorrhagic nephritis but also for nephrosis. According to results of clinical and bacteriologic examinations, 39 per cent of these patients had definite infections of the upper respiratory tract, such as enlarged and infected tonsils, recurrent infection of adenoids, adenitis,

4. Baeza-Goñi: La glomerulonefritis en la infancia, Chile, Editorial Zig-Zag, 1942; La nefrosis en la infancia, read before the Pan-American Pediatric Congress, Washington, D. C., July 1947.

sinusitis, otitis media and mastoiditis. Active lesions of streptococcic impetigo or staphylococcic pyodermitis were seen in 21.4 per cent of patients. Five per cent had bloody diarrhea, and cultures of their

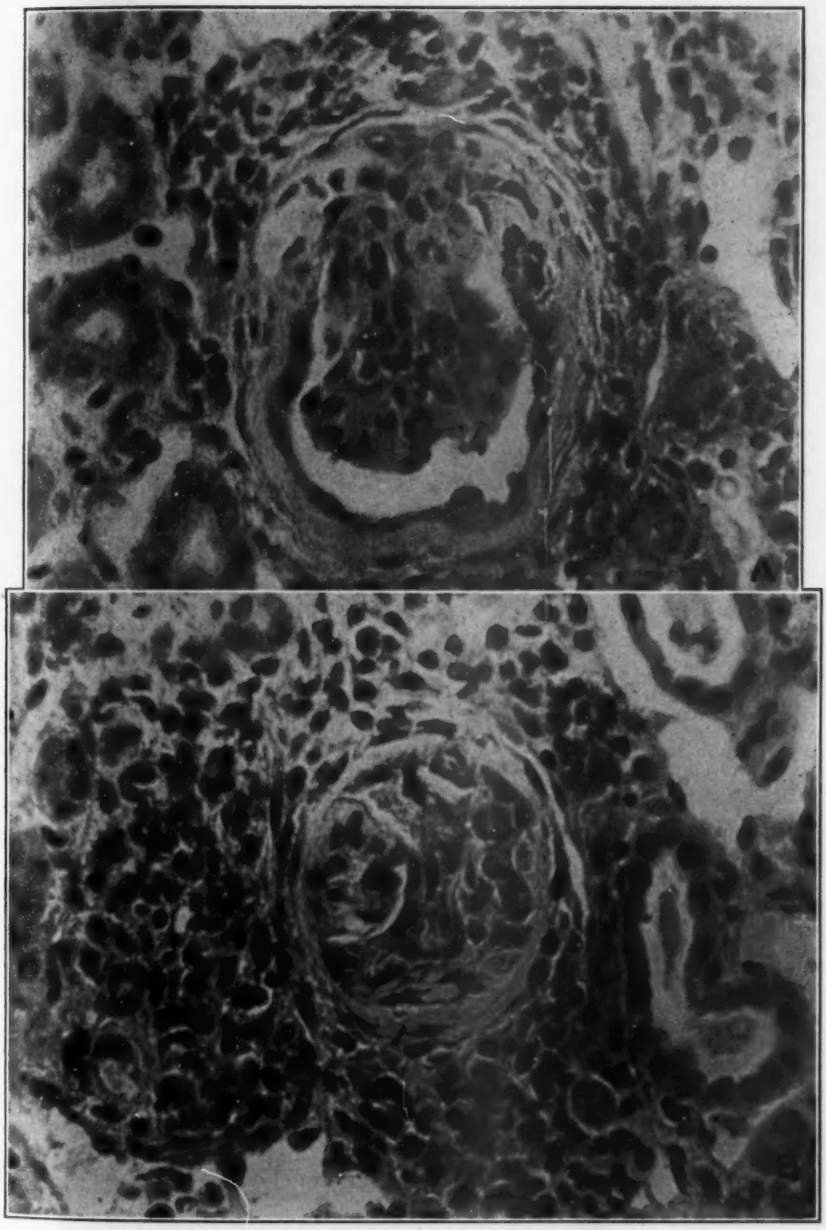

Fig. 4 *A* and *B*.—Photomicrographs showing thickening of basement membrane and glomerular capsule. Cellular infiltration around glomerular capsule is also evident (*B*).

stools yielded Salmonella or Shigella bacilli. Positive reactions to tests for syphillis were reported for ony 6 children. One child became edematous after having staphylococcic parotitis, and recurrence of edema was always preceded by swelling of the left parotid gland and purulent discharge from the salivary duct. Infection was not demonstrated for 19 patients, or 22.6 per cent (fig. 1). Bacterial infection was also the commonest complication and the factor responsible for the high mortality rate during the early stages of nephrosis. Pneumococcic peritonitis was clinically and bacteriologically diagnosed for 24 of a total of 66 children. One of these children in two years of illness had 6 infections of pneumococcic peritonitis and 1 of Escherichia coli peritonitis, as well as 1 of pneumococcic meningitis. Routine abdominal

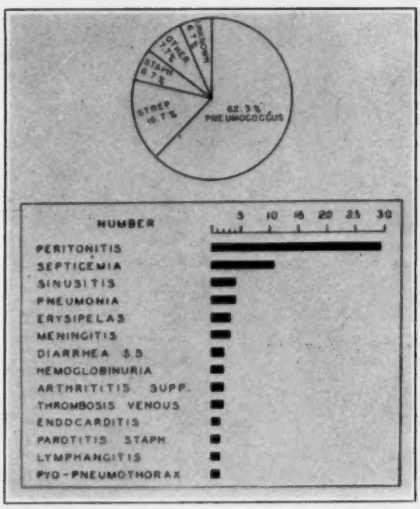

Fig. 5.—Graph showing incidence of bacterial infection in 84 cases of nephrosis.

taps and culture of ascitic fluid from all children having abdominal pain, fever and leukocytosis demonstrated the frequent occurrence of this complication in nephrosis. Septicemia (with cultures of the blood yielding pathogens) was present in 11 patients. Infection with Pneumococcus was followed, in order of frequency, by infections with Streptococcus and Staphylococcus. E. coli peritonitis was seen in 3 and Salmonella septicemia in 2 children (fig. 5). In treatment, intraperitoneal injections of penicillin for pneumococcic infections and of streptomycin for infections with E. coli and Salmonella gave the best results.[5]

5. Penicillin, 100,000 Oxford units, and streptomycin, 250 to 500 mg., were given in single injections and repeated if necessary at twenty-four hour intervals for two to four days, according to the infecting micro-organism.

A 3 year old boy had nocturnal hemoglobinuria resembling the Marchiafava-Micheli syndrome while receiving ammonium chloride by mouth. He became dehydrated, and examination showed carbon dioxide–combining power of 18 volumes per cent, fever and severe anemia, while leukocytes numbered 32,000. A few loose stools occurred from which Salmonella cholerasuis was cultured. Cultures of ascitic fluid, peripheral blood, blood from the sternal bone marrow and catheterized urine also showed the organism. A few days later an extensive thrombosis of the inferior vena cava (fig. 6) and purulent arthritis of the left coxofemoral joint developed. Pus from the joint was cultured, and the same micro-organism was recovered. Treatment with a combination of penicillin, sulfadiazine and heparin and blood transfusions brought about recovery in five months.

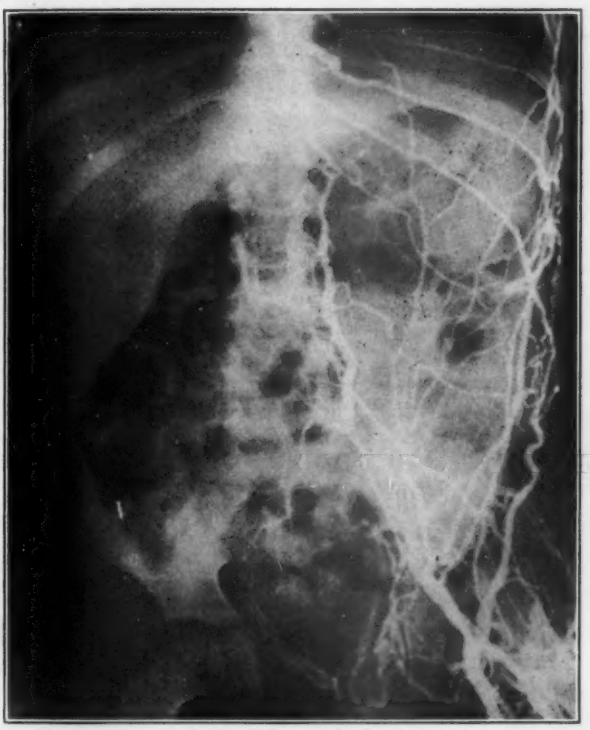

Fig. 6.—Roentgenogram showing thrombosis of inferior vena cava in the course of septicemia caused by Salmonella cholerasuis in a patient (M. J. B.) 3 years of age with nephronephritis. (Venogram with iodopyracet visualization.)

Mortality rate from bacterial infection previous to introduction of sulfonamide drugs and penicillin was 25.5 per cent in a total of 43 cases.[2] After introduction of these new drugs, the mortality rate was reduced to only 13.5 per cent (fig. 1).

Pathogenesis of nephrotic edema and its metabolic disturbances (hypoproteinemia and hypercholesteremia) are not well understood. The simple mechanism of albuminuria and hypoproteinemia cannot be accepted as the only factor responsible for the pathogenesis of

nephrotic edema because such a basis is often contradicted by clinical observations and by failure of protein therapy. The physiochemical characteristics of nephrotic edema are similar to those of nutritional edema and experimental plasmapheresis,[6] but its pathogenesis is unquestionably more complicated.

In a total of 469 determinations of albuminuria, the average concentration was 8.31 Gm. per thousand cubic centimeters of urine, while the highest concentration was 43 Gm. However, according to total daily diuresis, average for actual albuminuria during the edematous

TABLE 2.—*Concentration and Actual Excretion of Albumin During Active Edematous Stage of Nephrosis*

Patients	No. of Determinations	No. of Days of Observation	Total Albuminuria, Gm.		Daily Albuminuria, Gm.			
					× 1,000		Actual	
			× 1,000	Actual	Mean	Maximum	Mean	Maximum
P. C.	14	7	24.0	2.55	3.40	..	0.36	....
J. A. M.	21	21	96.8	21.74	4.47	27	1.03	5.13
J. M.	49	49	351.0	71.60	7.16	..	1.46	....
R. F.	45	45	355.0	25.60	7.90	36	0.56	2.00
R. A.	56	56	202.9	80.00	3.62	13	1.42	6.55
R. S. M.	14	14	44.8	4.90	3.20	15	0.35	1.84
F. M.	18	18	.....	17.80	....	..	0.98	1.10
L. C.	30	30	100.4	19.75	3.34	10	0.65	2.00
J. L. F.	94	94	1,224.7	531.60	13.02	35	5.65	14.91
O. O.	20	10	223.8	43.20	22.38	32	4.31	7.02
A. V. O.	12	12	97.0	25.04	8.08	13	2.08	4.08
M. N.	96	96	1,424.5	523.20	14.83	43	5.45	17.42
12	469	452	4,141.9	1,350.02	8.31	43	2.02	17.42

The Shevky-Stafford Albuminometer was used for these determinations. Tests were done in duplicate, with use of 1:10 dilution of urine. Values for actual albuminuria are based on daily diuresis. The last 3 patients received a total of 880, 500 and 900 cc., respectively, of low sodium concentrated plasma albumin intravenously without beneficial effect on the edema. Proteinuria was higher than usual during the injections of concentrated plasma albumin.

stage was 2.02 Gm. and the highest proteinuria observed was 17.42 Gm. per day (table 2).

No close relation was demonstrated between the albuminuria and hypoproteinemia and the edema. Proteinemia (total protein and plasma albumin) was lower in several cases after disappearance of edema. High doses of concentrated plasma or human serum (as much as

6. Leiter, L.: Experimental Edema, Proc. Soc. Exper. Biol. & Med. **26**:173 (Oct.) 1928; Experimental Nephrotic Edema, Arch. Int. Med. **48**:1 (July) 1931; Nephrosis, Medicine **10**:135 (May) 1931. Epstein, A. A.: The Nephroses, Bull. New York Acad. Med. **13**:621 (Nov.) 1937; Concerning the Causation of Edema in Chronic Parenchymatous Nephritis: Methods for Alleviation, Am. J. M. Sc. **154**:638 (Nov.) 1917; Further Observations on the Nature and Treatment of Chronic Nephrosis, ibid. **163**:167 (Feb.) 1922.

3,000 cc.) failed to decrease the edematous condition of a large number of patients and did not always increase the protein concentration in plasma. Edema reappeared in patients receiving a high protein diet free from salt with severe restriction of fluids.

Linder, Lundsgaard and Van Slyke,[7] in an extensive study of proteinemia and albuminuria in nephritis and nephrosis, observed no constant connection between changes in proteinemia and changes in the degree of edema. Many low concentrations were seen at times that no edema was present (p. 897). They stated:

Although the lowest figures for the plasma protein concentration were obtained when some edema was present, yet the greatest decrease in concentration did not

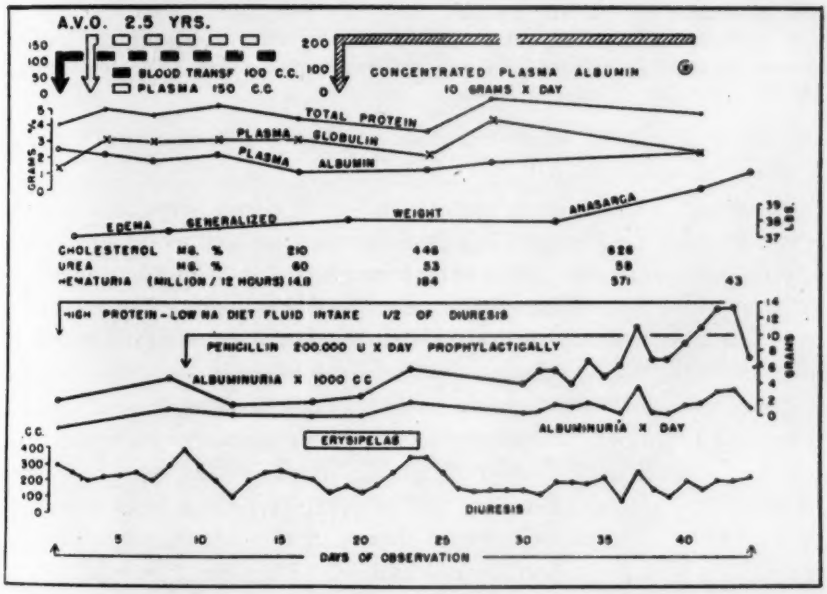

Fig. 7.—Chart illustrating failure of protein therapy in the nephrotic type of edema. The patient received 800 cc. of citrated blood, 900 cc. of plasma and 210 Gm. concentrated albumin (20 cc. contained 5 Gm. of albumin, and was equivalent to 100 cc. of plasma). Plasma proteins remained below normal values. Weight and edema increased at the end of treatment. The same results were observed in 4 additional patients given concentrated plasma albumin.

correspond with the greatest edema and a very considerable decrease was compatible with absence of recognizable edema. (p. 914)

Low plasma protein concentrations were always associated with considerable losses of protein in the urine, but these losses did not provide an explanation for all our observations. A disturbance in the production of the plasma protein appears probable. (p. 919.)

7. Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: The Concentration of Plasma Proteins in Nephritis, J. Exper. Med. **39**:887 (June) 1924.

In 5 cases of nephrosis they recorded 7 Gm. per day as the highest albuminuria.

Salt intake during the active stage of nephrosis was observed to increase the excretion of albumin in urine and the deposition of edema. The following report is demonstrative:

Patient G. T., 5 years of age, twelve days previous to ingestion of salt showed: total plasma protein, 5.33 Gm., albumin, 2.15 Gm. and globulin, 3.18 Gm., per hundred cubic centimeters. Total diuresis in twelve days was 4,710 cc.; total albuminuria in twelve days was 0.55 Gm. (total concentration, 6.06 Gm. $\times$ 10^{3}). Weight decreased from 69 to 47.5 pounds (31.3 to 21.5 Kg.). Weight increased to 63 pounds (28 Kg.) with deposition of edema after patient received 2.5 Gm. of salt daily for fifteen days. Diuresis totalled 7,545 cc.; total albuminuria in fifteen days was 33.6 Gm. (concentration, 56.8 Gm.); total plasma protein measured 5.12 Gm., albumin, 1.73 Gm. and globulin, 3.39 Gm., per hundred cubic centimeters. The hematocrit reading was 64 per cent of plasma volume. Chloride in plasma increased only from 360 to 400 mg. and in the red blood cells from 200 to 240 mg., per hundred cubic centimeters.

Similar observations were reported by Widal, Lemiere and Pasteur Vallery-Radot.[8]

Increase in albuminuria and deposition of edema were also repeatedly noticed in the course of bacterial infection, as well as disappearance of these symptoms after intercurrent infection was definitely controlled, although patients maintained the same basal conditions. On the other hand, disappearance of edema and dehydration were observed in a few instances after severe infections, which were followed by a spontaneous and unexplainable improvement in the metabolic disturbances characteristic of nephrosis. However, such an improvement, which was also observed with measles either occurring spontaneously or induced by inoculation, did not mean that the nephrotic syndrome was definitely cured. Long-standing observation showed this improvement to be only temporary in a great number of children. Recurrence of edema was seen as late as ten months after an apparent cure. A spontaneous crisis of polyuria, with total elimination of edema and normalization of proteinemia and lipemia, occurred in 2 children without previous infection or medical treatment.

Persistence of hypoproteinemia and hypercholesteremia was seen in children both in and out of the edematous stage and with and without albuminuria during all the time of active nephrosis. A comparative analysis of protein and cholesterol concentrations in the renal venous blood from 2 edematous children is presented in table 3. No conclusions can be drawn from this short observation, but higher cholesterol and lower cholesterol ester concentrations in the renal venous blood, as com-

8. Widal, F.; Lemiere, A., and Pasteur Vallery-Radot: Syndrome de retention chloruré, in Roger, G. H.; Widal, F., and Teissier, P. J.: Nouveau traité de médecine, Paris, Masson & Cie, 1926, no. 17, pp. 57-145.

pared with results from simultaneous determinations on the peripheral blood, are significant. As far as treatment of nephrosis is concerned, no one procedure yielded satisfactory results persistently enough to encourage its routine use in all cases of the disease. Prophylaxis and treatment of bacterial infections, rest in bed during the active edematous stage, proper diet (high in vitamins and protein and free from salt, with low intake of fluid) and intravenously administered protein therapy (plasma concentrated human serum and whole blood) comprised, in general, the care given these patients.

II. CLEARANCE AND SATURATION TESTS

Failure of protein therapy led to the belief that hypoproteinemia was not the only responsible factor in the deposition of nephrotic edema. In 1943,[2] I advanced the possibility of increased tubular

TABLE 3.—*Protein and Cholesterol Concentrations in Blood from Renal Vein of Nephrotic Children;* A Comparative Analysis with Peripheral Blood*

Patient	Sample of Blood	Total Protein, Gm./100 Cc.	Plasma Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Cholesterol, Mg./100 Cc.	Cholesterol Ester, Mg./100 Cc.
R. F.....	v. b.†	4.26	1.99	2.27	450	390
	R. V.	3.87	1.92	1.95	520	150
	A. a.	3.76	1.92	1.84	460	398
R. A. D.....	v. b.	5.56	2.15	3.41	608	409
	A. b.	5.56	2.44	3.12	619	309.5
	R. V.	5.56	2.06	3.50	670	189
	v. a.	5.33	2.06	3.27	652	488
	A. a.	5.56	2.00	3.56	650	423

* Examinations performed in 2 nephrotic children operated on for decapsulation of kidney.
† v. b. and A. b. indicate peripheral venous and arterial blood before operation; R. V., blood from renal vein; v. a. and A. a., peripheral venous and arterial blood after operation.

reabsorption as another renal factor involved in the formation of edema. Hematocrit readings and calculations of plasma volume by the Evans blue dye method showed a normal or high fraction of plasma in the blood of these patients. With the exception of the vascular factor in nephrosis with glomerular lesions, these observations failed to show a decreased glomerular filtrate secondary to escape of fluid and electrolytes to interstitial spaces. Extrarenal influences of hypoproteinemia should not interfere with the glomerular filtration rate in a situation opposite to that of dehydration. Therefore, I considered that inulin clearance tests performed both in and out of the edematous stage would give a more satisfactory explanation of kidney's influence on the pathogenesis of nephrotic edema. Actually, in the light of new clearance and saturation tests the improved knowledge of kidney's physiopathologic functions is an important step in the study of this subject.

In previous communications[9] my associates and I reported the results of these tests for normal children. They were similar to those recorded by Smith and associates[10] and by Goldring and Chasis[11] in normal adults except for tubular reabsorption. Tests for maximal tubular reabsorptive capacity for glucose in normal children yielded higher figures than those reported by Shannon and associates[12] and Smith[10b] in adults. The mean value for children was 543 mg. per minute.[13]

Glucose does not seem to be the ideal substance for the estimation of tubular reabsorptive capacity, at least in children with normal or

9. Galán, E.: Las pruebas renales de aclaramiento y saturación: I. Conceptos generales; II. Interpretación y crítica; Observaciones personales, Rev. cubana pediat. **19**:100 (Feb.); 138 (March) 1947. Pérez-Stable, M.: La prueba de inulina en niños normales, Arch. de med. inf. **16**:89 (June) 1947. Galán, E.; Pérez-Stable, M.; Más Martin, J., and García Fáez, O.: Las pruebas renales de aclaramiento y saturación en el niño normal, ibid. **16**:102 (June) 1947.

10. (*a*) Smith, H. W.: The Physiology of the Kidney, London, Oxford University Press, 1938; (*b*) Lectures on the Kidney (Porter and W. H. Lectures) University of Kansas, University Extension Division, 1943. (*c*) Smith, H. W.; Goldring, W., and Chasis, H.: The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, J. Clin. Investigation **17**:263 (May) 1938.

11. Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease, New York, The Commonwealth Fund, 1944, chap. 4, pp. 53-73; Appendix D, pp. 195-207; Appendix G, pp. 218-241.

12. (*a*) Shannon, J. A., and Fisher, S.: The Renal Tubular Reabsorption of Glucose in the Normal Dog, Am. J. Physiol. **122**:765 (June) 1938. (*b*) Shannon, J. A.; Farber, S., and Troast, L.: The Measurement of Glucose Tm in the Normal Dog, ibid. **133**:752 (July) 1941. (*c*) Shannon, J. A.: Renal Tubular Excretion, Physiol. Rev. **63**:93 (Jan.) 1939.

13. Smith[10b] demonstrated that in the normal adult kidney maximal tubular reabsorptive capacity for glucose is greatly dependent on the glomerular filtration rate. He said:

A positive correlation between Cin and TmG is rather to be anticipated in view of the functional relationship which, in the interest of glucose conservation, we may expect to find between any glomerulus and its nephron (p. 99).

According to Smith, the ratio of glomerular filtration rate to tubular reabsorptive capacity for glucose was 0.371 for men and 0.395 for women. The correlation coefficient (r) was + 0.656 in men and + 0.048 in women. He was of the opinion that this lack of correlation in women was fortuitously related to the smallness of sample. Both terms have a relatively narrow dispersion, especially that for women, a circumstance contributing to uncertainty concerning the coefficient of correlation. Therefore, high values for tubular reabsorptive capacity for glucose are usually obtained with high glomerular filtration rates and vice versa. The same correlation between maximal tubular reabsorptive capacity for glucose and glomerular filtration rate is to be expected in normal children. However, the coefficient of correlation, though higher in children than in women, also showed a low value (r: + 0.061). The present series of children was also too small (16 cases) to warrant confident conclusions for correlation of tubular reabsorptive capacity for glucose and glomerular filtration rate. Further determinations of maximal tubular reabsorptive capacity for glucose in normal children have to be

diseased kidneys. Saturation of the nephron with glucose is difficult to accomplish without untoward effects. It increases the volume of blood and diuresis, and it also is quickly metabolized. Its high diffusibility causes some extrarenal clearance, especially in edematous conditions. Glucose metabolism is not usually interfered with by the diseased kidney except in renal diabetes. As Smith stated,

> . . . the tubular reabsorptive capacity is roughly proportional to the filtration rate . . . One cannot generalize from the reabsorption of glucose to the reabsorption of chloride, urea, water and other substances.

These considerations led to simultaneous determinations of tubular reabsorption of chlorides, urea and water in children. Criticism of these tests is not ignored, but the importance of these substances in edema and nephritis is obvious. Simultaneous determination of tubular reabsorptive capacity for chlorides in children showed a close relation to the tubular reabsorptive capacity for glucose. The ratio of tubular reabsorptive capacity for glucose to that for chlorides was 1.07 in normal children. I also feel that the fraction of glomerular filtrate reabsorbed per unit of active tubular epithelium can be better estimated by calculation of values for the ratios of tubular capacities for glucose and chlorides to the glomerular filtration rate and for the ratio of the glomerular filtration rate to urea clearance, as well as for per cent of (Cin-V),[14] under the same basal conditions. The ratio of tubular reabsorptive capacity for glucose to the glomerular filtration rate in normal children was higher (4.35) than in adults, as calculated from Smith's data (2.75 for men and 2.63 for women; pp. 96-97 [10b]).

A total of 156 tests [15] were performed for 5 children with acute hemorrhagic nephritis and for 14 with the nephrotic syndrome. The

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made in order to confirm or modify the high figure obtained in this study, although it was provisionally accepted as a standard reference for such a determination in cases of renal disease. However, since the glomerular filtration rate of children is similar to that of adults, a higher tubular reabsorptive capacity for children should be expected in view of their lower urinary output.

14. Cin indicates values for glomerular filtration rate. For explanation of value V, see footnote to table 4.

15. Tests were performed according to procedures advised by Smith, Goldring and Chasis (footnotes 10 *b* and 11) and Shannon and others [12]: 50 cc. vials of 10 per cent pyrogen-free inulin (U. S. Standard Products Co., Woodworth, Wis.) were used for the 156 determinations of glomerular filtration rate; 30 cc. vials of 35 per cent iodopyracet injection U.S.P. ("diodrast" containing 49.8 per cent iodine per gram) were used for the 22 determinations of clearance and tubular excretion of iodopyracet, and 500 cc. of 50 per cent glucose solution (Linner and Vieta Plasencia Laboratories, Habana, Cuba) was used for the 58 determinations of tubular reabsorption capacity for glucose. In addition, 63 determinations for tubular reabsorptive capacity for chlorides, 61 for plasma urea clearance and 17 for exogenous creatinine (administered by mouth) were made.

Plasma concentration of iodine from iodopyracet fluctuated between 0.5 and 2.5 mg. per hundred cubic centimeters for clearance of iodopyracet and ranged above 30

(Footnote continued on next page)

TABLE 4.—*Results of Studies on Patients with Glomerulonephritis*

Name, Age, Sex, Surface Area Factor, Date	V *	Glomerular Filtration Rate, Cc./Min.	Tubular Reabsorption of Glucose, Mg./Min.	Tubular Reabsorption of Chloride, Mg./Min.	Rate of Iodopyracet Clearance, Cc./Min.	Tubular Excretion of Iodopyracet, Mg./Min.	Urea Clearance, Cc./Min.	Comment
C. M. 11 yr. M 1.3 August 1946	3.1	54.8	.....	261.1	51.5	0	22.9	150,000,000 red blood cells in blood pressure, 170 systolic 100 diastolic; total protein Gm./100 cc.; cholesterol, 17 100 cc.; enlargement of + edema; treated with choline and transfusion; pressure, 125 systolic and tolic; 3,000,000 red blood urine
	3.7	63.3	.....	270.9	51.6	0	27.1	
	4.5	62.4	.....	246.1	42.7	0	24.4	
	4.6	35.8	.....	.....	....	..	....	
	4.0	36.4	.....	.....	....	..	....	
	4.3	20.1	.....	.....	....	..	....	
	3.9	20.0	.....	122.3	50.7	0	13.6	
	8.0	65.8	.....	217.1	136.8	..	15.4	
	8.9	56.1	.....	216.8	140.3	..	....	
	0.9	20.3	.....	.....	....	..	....	
	0.8	26.5	.....	.....	....			
	1.3	41.3	.....	.....	....	..	24.7	
	1.8	14.1	213.6	69.7	....	..	....	
	3.6	25.6	100.6	.....	....	..	15.4	
	4.2	22.9	205.4	79.3	....	..	....	
	3.3	16.8	.....	.....	....			
C. N. 10 yr. M 1.4 July 1946	5.2	96.0	.....	346.1	....	..	54.3	Gross hematuria; blood 98 systolic and 65 diastolic; protein, 6.8 Gm./100 cc.; terol, 190 mg./100 cc.; mg./100 cc.; plasma 3.5 Gm./100 cc.; treatment: cillin, 500,000 units
	4.8	79.2	.....	259.5	....	..	53.6	
	5.4	83.2	.....	278.1	....	..	43.9	
	7.1	87.4	.....	.....	....	..	....	
	5.6	64.3	.....	.....	....	..	....	
	6.4	75.3	.....	.....	....	..	....	
	8.0	87.3	516.3	264.4	....	..	60.9	
	7.8	99.1	509.9	290.5	....	..	44.6	
	7.5	88.2	.....	309.2	642.5	45	38.5	
O. Q. M. 7 yr. M 2.5 October 1946	0.5	51.6	.....	.....	....	..	....	36,000,000 red blood cells in blood pressure, 138 systolic 100 diastolic; ++ edema; 98 mg./100 cc.; total protein Gm./100 cc.; +++ syphilis; ment: penicillin, 5,000,000
	0.2	27.3	.....	.....	....	..	....	
	0.4	51.8	.....	.....	....	..	....	
	0.8	61.2	.....	.....	....	..	....	
	0.8	82.0	.....	.....	....	..	....	
	0.6	103.0	.....	.....	....	..	....	
G. R. A. 9 yr. M 1.8 August 1946	0.3	28.6	.....	.....	....	..	....	Gross hematuria; + edema; pressure, 132 systolic diastolic; urea, 100 mg./ total protein, 6.8 Gm./ cholesterol, 200 mg./ xanthoproteic test, 70 per
	0.4	52.0	.....	.....	....	..	....	
	0.3	34.0	.....	.....	....	..	....	
	0.8	79.0	.....	.....	....	..	....	
O. E. L. 7 yr. M 1.9 December 1946	6.8	162.0	394.7	.....	....	..	....	Convalescent; 5,000,000 red cells in urinary sediment; protein, 6.8 Gm./100 cc.; terol, 190 mg./100 cc.
	5.1	102.0	380.7	.....	....	..	....	

* V indicates values for flow of urine corrected to a surface area of 1.73 square meters; observed flows may be calcula dividing by the surface area factor given in the first column.

mg. for tubular excretory capacity for iodopyracet. Saturation of nephron with glucose was accomplished by raising its load to above 1.5 (600 mg. per hundred cubic centimeters or more in plasma of arterial blood). Urea was calculated in "maximal plasma clearance" $\left(\frac{U}{P}\right)\sqrt{2V}$ for diureses below 2 cc. per minute (U indicates mg. of urea per hundred cubic centimeters of urine, P, mg. of urea per hundred cubic centimeters of plasma and V, cubic centimeters of urine per minute). Figures were corrected for surface area of patient. Doses were regulated according to the age of the patient.

The analytic method of Hubbard and Loomis (*J. Biol. Chem.* **146**:641 [Oct.] 1942) derived from Roe's quantitative modification of Selivanoff's reaction for levulose was adapted for the photocolorimeter for inulin determination (no yeasting of plasma glucose was necessary, thus avoiding inulinoid blank except for simultaneous inulin-glucose test). The photocolorimetric method of Flox, Pitesky and Alving (*J. Biol. Chem.* **142**:147 [Jan.] 1942) was used for iodopyracet determinations; Van Slyke's gasometry method for determination of urea and his silver method to date for chlorides were also used.

last group was subdivided, according to the results of clinical and laboratory examinations, into 5 children with nephronephritis (nephrotic syndrome plus hematuria and/or hypertension) and 9 with noncomplicated nephrosis. Tests were performed on patients both in and out of the edematous stage of nephrosis. Results (tables 4 to 8) may be summarized as follows:

TABLE 5.—*Results of Studies on Patients with Nephronephritis*

V*	Glomerular Filtration Rate, Cc./Min.	Tubular Reabsorption of Chloride, Mg./Min.	Rate of Iodopyracet Clearance, Cc./Min.	Tubular Excretion of Iodopyracet, Mg./Min.	Urea Clearance, Cc./Min.	Comment
0.10	30.9	.....	.....	....	....	Total plasma protein, 4.8 Gm./100 cc.; cholesterol, 666 mg./100 cc.; blood urea, 102 mg./100 cc.; 24,000,000 red blood cells in urine; blood pressure, 110 systolic and 75 diastolic; +++ edema
1.35	106.3	.....	.....	....	....	
0.67	61.1	.....	.....	....	....	
0.20	17.4	.....	.....	....	....	
2.50	47.7	.....	.....	....	....	
1.30	24.3	.....	.....	....	....	No edema; urea, 98 mg./100 cc.; blood pressure, 90 systolic and 60 diastolic; total plasma protein, 4.4 Gm./100 cc.; microscopic hematuria
2.15	78.8	.....	.....	....	....	
1.17	30.6	.....	.....	....	....	
8.60	87.0	.....	.....	....	....	
2.15	110.0	.....	.....	....	....	
1.10	126.0	.....	.....	....	....	
3.30	119.0	.....	.....	....	....	
0.01	31.9	.....	.....	....	....	Total plasma protein, 3.76 Gm./100 cc.; plasma albumin, 1.5 Gm./100 cc.; cholesterol, 571 mg./100 cc.; 8,000,000 red blood cells in urine; ++ edema
0.01	34.9	.....	.....	....	....	
0.08	20.9	.....	.....	....	....	
2.05	91.3	752.2	.....	....	27.3	Total plasma protein, 5.12 Gm./100 cc.; cholesterol, 1,000 mg./100 cc.; 38,000,000 red blood cells in urine; urea, 98 mg./100 cc.; +++ edema; CO_2-combining power, 27 vol. per cent; blood pressure, 98 systolic, and 65 diastolic; xanthoproteic test, 30 per cent; coma; death; autopsy: glomerular lesions, enlarged and smooth kidneys
3.50	142.5	695.9	.....	....	38.9	
3.63	136.6	668.6	.....	....	43.2	
0.21	34.5	.....	282.7	....	12.6	
0.15	62.6	349.8	349.8	....	35.5	
0.19	47.9	.....	.....	2.84	....	
0.40	61.8	.....	.....	1.83	....	
0.39	53.8	.....	.....	1.53	....	
0.22	27.3	.....	.....	....	....	Total protein, 3.4 Gm./100 cc.; gross hematuria; urea, 154 mg./100 cc.; cholesterol, 500 mg./100 cc.; ++ edema; blood pressure, 110 systolic and 75 diastolic; phenolsulfonphthalein test, 55 per cent; hematocrit reading, 74 per cent of plasma volume
0.28	29.0	.....	.....	....	....	
0.29	36.4	.....	.....	....	....	
0.33	35.5	.....	.....	....	....	
0.05	48.4	.....	.....	....	47.4	Total protein, 5.8 Gm./100 cc.; +++ edema; plasma albumin, 2.06 Gm./100 cc.; urea, 45 mg./100 cc.; Salmonella cholerasuis septicemia; hemoglobinuria plus gross hematuria; thrombosis of inferior vena cava; Salmonella cultured from ascitic fluid and urine
0.06	68.4	.....	.....	....	63.0	
0.10	33.8	.....	.....	....	....	

*e footnote to table 4.

Acute Hemorrhagic Nephritis.—A decrease in effective renal plasma flow, glomerular filtration rate and tubular excretrory and reabsorptive capacity was seen in the acute hypertensive stage of glomerulonephritis. Improvement in renal function was observed after blood pressure dropped to normal. A relative and absolute decrease in tubular reabsorption was an interesting observation in these patients. Lower values for tubular reabsorptive capacities for glucose and chlor-

TABLE 6.—*Result of Studies on Patients with Nephrosis*

Name, Age, Sex, Surface Area Factor, Date	V*	Glomerular Filtration Rate, Cc./Min.	Tubular Reabsorption of Glucose, Mg./Min.	Tubular Reabsorption of Chloride, Mg./Min.	Iodopyracet Clearance, Cc./Min.	Tubular Excretion of Iodopyracet, Mg./Min.	Urea Clearance, Cc./Min.	Creatinine Clearance, Mg./100 Cc.	Comment
L. L. 7 yr. M 2.3 November 1945	0.64 0.62 0.26 0.39	297.0 246.0 149.0 140.0	.....	.....	.....	.....	.....	.....	Total plasma protein, 3.5 Gm./100 cc.; 6,000,000 red blood cells in urine; blood urea, 45 mg./100 cc.; no edema; blood pressure, 90 systolic and 55 diastolic; cholesterol, 450 mg./
J. E. 5 yr. M 3.0 December 1946	2.40 2.65 0.38 0.78	125.0 135.0 140.0 120.0	.....	.....	.....	.....	.....	.....	++ edema; 212,500 red blood cells in urinary sediment; hematocrit, 42 per cent cells; transfusion; death
M. L. 2 yr. F 3.0 November 1946	0.15 0.20	164.0 208.0	.....	.....	.....	.....	.....	.....	+++ edema; no hematuria; total protein, 4.7 Gm./100 cc.; cholesterol, 571 mg./100 cc.; blood pressure, 100 systolic and 65 diastolic
R. A. D. 10 yr. M 1.78 March 1946	0.34 0.25 0.14 0.11 0.96 0.63 0.40 0.77 1.90 2.00 2.10 1.10 0.64 0.50 0.27 0.19 1.30 1.10 1.06 2.60	122.4 130.1 104.9 121.1 165.2 184.6 133.6 147.0 205.2 162.4 172.7 164.1 71.5 67.5 56.9 79.3 93.4 61.1 97.9 123.2	375.6 331.6 .... 654.4 598.9 576.2 449.3 880.9 849.4 754.8 818.3 251.4 226.5 441.7 ..... 356.0 379.8 374.3 573.0	753.0 775.0 778.0 ..... 450.6 456.1 697.6 .... 985.2 ..... 382.0 354.0 383.0 372.0 473.3 476.4 468.6 434.8	.....	.....	71.3 96.7 78.6 87.9 69.6 ..... 86.5 ..... 58.7 46.5 45.5 61.6 49.5 52.3 ..... 68.0 60.4 ..... 95.5 103.9	114.7 112.6 175.6 ..... 173.2 ..... 147.8 226.3 232.6 184.4 176.1 212.6 146.0 153.0 138.0 ..... 161.0 157.3 207.9 207.0	+++ edema; total protein Gm./100 cc.; plasma albumin 2.5 Gm./100 cc.; cholesterol mg./100 cc.; urea, 38 mg./ No edema; total protein Gm./100 cc.; plasma albumin 2.15 Gm./100 cc.; 50,000 blood cells in urine; blood pressure, 90 systolic and 65 diastolic No edema; biopsy specimen kidney: no glomerular lesion +++ edema; total protein Gm./100 cc.; plasma albumin 2.3 Gm./100 cc. No edema; blood pressure systolic and 60 diastolic hematuria; total protein Gm./100 cc.; plasma albumin 1.45 Gm./100 cc.; cholesterol 500 mg./100 cc.
P. B. 3 yr. F 2.70 May 1946	3.25 3.50 5.50 6.75 5.10 8.70 11.20	90.0 79.4 106.4 129.0 87.4 102.6 122.4	654.9 880.1 575.3 413.9 730.4 687.0 669.0	567.8 512.1 445.1 413.5 433.5 827.6	.....	.....	87.7 58.8 68.3 61.2 ..... 96.2	....	No edema; no hematuria; plasma protein, 4.5 Gm./100 cc.; blood pressure, 90 systolic 60 diastolic; cholesterol mg./100 cc. ++ edema; urea, 30 mg./100 cc.; total protein, 3.3 Gm./100 cc.; plasma albumin, 2 Gm./100 cc.; cholesterol, 500 mg./100 cc.
A. G. 5 yr. M 2.0 February 1946	3.00 4.00 6.00 4.50 0.30 0.50	101.2 148.0 152.0 128.7 60.6 60.5	....	694.0 659.8 599.1 ..... 364.6 326.9	.... 776.0	.... 20.8	58.0 53.5 70.6 ..... 21.2	....	+++ edema; total protein Gm./100 cc.; cholesterol mg./100 cc.; bacillary dysentery; blood urea, 31 mg./100 cc.; no hematuria
E. G. 2 yr. M 2.9 September 1946	0.35 0.11 0.19 0.16 0.08 0.04 0.07 0.08	114.0 102.0 166.0 245.0 237.8 148.5 165.2 147.0	....	....	....	....	....	....	Total protein, 4.26 Gm./100 cc.; plasma albumin, 2.05 Gm./100 cc.; cholesterol, 740 mg./100 cc.; blood pressure, 90 systolic 60 diastolic; no hematuria +++ edema; urea, 64 mg./100 cc.
P. B. 3 yr. M 2.7 March 1946	0.44 0.57 1.00 1.27	174.6 140.0 138.5 124.0	....	682.5 599.8 538.3 531.0	643.0 560.0 ..... 910.0	.... 48.7 69.0	41.8	....	Total protein, 3.56 Gm./100 cc.; plasma albumin, 2.04 Gm./100 cc.; cholesterol, 500 mg./100 cc.; 200,000 red blood cells in urine; no edema

* See footnote to table 4.

TABLE 6.—*Result of Studies on Patients with Nephrosis—Continued*

ne, Sex, ace ra tor, ate	V *	Glomerular Filtration Rate, Cc./Min.	Tubular Reabsorption of Glucose, Mg./Min.	Tubular Reabsorption of Chloride, Mg./Min.	Iodopyracet Clearance, Cc./Min.	Tubular Excretion of Iodopyracet, Mg./Min.	Urea Clearance, Cc./Min.	Creatinine Clearance, Mg./100 Cc.	Comment
. D. yr. M 78 ril 46	1.50	157.3	.....	852.5	.....	.....	55.6	.....	Total protein, 5.56 Gm./100 cc.; plasma albumin, 2.68/100 cc.; globulin, 2.9 Gm./100 cc.; no hematuria; blood pressure, 90 systolic and 60 diastolic
	3.00	156.5	.....	819.4	697.5	35.5	71.8	.....	
F. yr. M 10 nary 46	1.20	144.7	551.5	588.0	.....	.....	52.7	.....	Total protein, 4.57 Gm./100 cc.; cholesterol, 444 mg./100 cc.; urea, 23 mg./100 cc.; no edema; no hematuria; blood pressure, 90 systolic and 60 diastolic
	0.90	108.5	528.4	572.0	.....	.....	21.7	.....	
	0.69	102.9	475.1	570.0	.....	.....	34.5	.....	
	0.56	132.7	541.9	554.0	.....	.....	50.9	.....	
	0.63	98.4	630.0	.....	.....	.....	....	.....	
	0.55	102.7	420.8	417.4	.....	.....	64.5	.....	+++ edema; total protein, 4.4 Gm./100 cc.; plasma albumin, 2.57 Gm./100 cc.; urea, 34 mg./100 cc.; cholesterol, 558 mg./100 cc.; 6 infections with pneumococcic peritonitis and 1 with pneumococcic meningitis; 5,000,000 red blood cells in urine
	0.24	75.7	288.5	.....	.....	.....	....	.....	
	0.24	76.5	265.6	.....	.....	.....	....	.....	
	0.17	66.1	291.0	452.6	.....	.....	....	.....	
	1.25	167.0	536.7	702.0	.....	.....	76.9	.....	
	0.48	122.0	457.1	653.0	.....	.....	77.0	.....	
	0.79	106.0	786.4	625.0	.....	.....	53.8	.....	
	0.82	134.0	770.0	.....	.....	.....	64.0	.....	
	1.40	33.6	317.4	.....	.....	.....	....	.....	Urea, 75 mg./100 cc.; biopsy specimen of kidney: thickening of glomerular capsule, vascular obliteration, cellular infiltration; total protein, 3.94 Gm./100 cc.
	3.70	77.7	250.5	.....	.....	.....	....	.....	
	2.30	49.6	387.5	.....	.....	.....	....	.....	
	2.30	49.6	402.7	.....	.....	.....	....	.....	
e T. yr. M 4 ne 46	0.39	156.0	610.4	831.1	.....	.....	75.0	.....	+++ edema; urea, 28 mg./100 cc. total protein, 6 Gm./100 cc.; plasma albumin, 1.5 Gm./100 cc.; cholesterol, 545 mg./100 cc.; blood pressure, 85 systolic and 55 diastolic
	1.05	142.0	750.0	834.0	.....	.....	78.0	.....	
	0.90	135.0	808.0	.....	847.0	53.0	70.6	.....	
	0.65	173.0	.....	.....	.....	.....	....	.....	
	0.60	123.0	.....	.....	.....	.....	....	.....	
	0.90	136.0	.....	.....	.....	.....	....	.....	
	4.60	168.0	530.0	.....	1,035.0	.....	....	.....	Decreasing edema
	5.10	152.0	607.0	.....	876.0	.....	....	.....	No edema; no hematuria; blood pressure, 90 systolic and 60 diastolic; total protein, 5.33 Gm./100 cc.; cholesterol, 675 mg./100 cc.
	6.00	140.0	533.0	.....	770.0	.....	....	.....	
	1.70	139.0	.....	.....	.....	75.5	....	.....	
	1.00	151.0	.....	.....	.....	60.0	....	.....	
	1.10	173.0	.....	.....	.....	66.6	....	.....	
	11.00	210.0	.....	722.0	816.0	72.0	....	.....	
	4.60	143.0	.....	787.0	796.0	72.6	....	.....	
	3.80	198.0	.....	.....	793.0	.....	....	.....	

*See footnote to table 4.

ides and for ratios of tubular reabsorptive capacities for glucose and chlorides to the glomercular filtration rate, as well as the ratio of glomerular filtration rate to urea clearance and per cent of (Cin-V), were obtained for all patients during the hypertensive stage as compared with those for normal children.

Rubin, Rapoport and Randall [16] reported similar results. Although these investigators did not determine the tubular reabsorptive capacity in nephritic children, they inferred, from the decreased glomerular filtration rate and rather good diuresis, that tubular reabsorption of water was decreased in acute hemorrhagic nephritis.

One of our patients (C. M.) showed no tubular excretion of iodopyracet and a sharp decrease in effective renal plasma flow approximating the decreased glomerular filtration rate (tables 4, 7 and 8).

16. Rubin, M. I.; Rapoport, M., and Randall, M.: Estimation of Renal Function in Children with Glomerulonephritis and Nephrosis, Am. J. Dis. Child. **69**:322 (May) 1945.

Nephronephritis.—All 5 children showed results similar to those observed in acute hemorrhagic nephritis except for tubular reabsorption ratios. No determination of tubular reabsorptive capacity for glucose and few determinations of tubular reabsorptive capacity for chlorides were done for these patients. Absolute values for tubular reabsorption of chloride and urea were lower than in normal children, in agreement with the simultaneous decrease in glomerular filtration rate. However, ratios of tubular reabsorptive capacity for chlorides to the glomerular filtration rate and of the glomeruler filtration rate to urea clearance as well as per cent of (Cin-V) showed higher values than those for children with hemorrhagic nephritis and for normal children (tables 5, 7 and 8).

Nephrosis (Without Glomerular Symptoms).—Normal or increased values for glomerular filtration rate, effective renal plasma flow and maximal tubular excretory and reabsorptive capacity were observed for 8 of 9 children with uncomplicated nephrosis. Values for tubular reabsorptive capacity for glucose, ratios of tubular reabsorptive capacities for glucose and chlorides to the glomerular filtration rate and of the glomerular filtration rate to urea clearance and per cent of (Cin-V) were higher than those for normal children and the children of the two previous groups.[17]

Emerson, Futcher and Farr[18] were the first to report high glomerular filtration rates in 3 nephrotic children with increased values

17. Results of calculation of the correlation coefficient of the ratio of tubular reabsorptive capacities for glucose and chlorides to glomerular filtration rate by the formula

$$r = \frac{\Sigma xy}{N\sigma_x \sigma_y}$$

were more satisfactory in the children with renal disorders than in the normal children. In those with nephritis, the correlation coefficient (r) of the ratio of tubular reabsorptive capacity of glucose to glomerular filtration rate was 0.993; in those with nephronephritis, the correlation coefficient of the ratio of tubular reabsorptive capacity of chlorides to glomerular filtration rate was 0.673; in those with nephrosis, the correlation coefficient of the ratio of tubular reabsorptive capacity of glucose to glomerular filtration rate was 0.603 and that of the ratio of tubular reabsorptive capacity of chlorides to glomerular filtration rate was 0.605.

Patient R. F. had 17 clearance and saturation tests performed during his five months at the hospital. Results were comparable to those for other children of this same group except for the last 4 tests, when a sharp decrease in glomerular filtration rate was observed. At this time a slight increase in red blood cells in the urine (to 5,000,000 cells) was noticed, and blood urea went up to 75 mg. per hundred cubic centimeters. A biopsy specimen of kidney showed a few areas of interstitial nephritis, vascular obliteration and hyaline thickening of the basement membrane and glomerular capsule (fig. 2 and tables 6 to 8).

18. Emerson, K., Jr.; Futcher, P. H., and Farr, L. E.: The Relation of High and Low Urea Clearance to Inulin and Creatinine Clearances in Children with the Nephrotic Syndrome, J. Clin. Investigation **20**:361 (July) 1941.

for urea clearance. In a total of 15 periods they recorded glomerular filtration rates of 129 to 327 cc. per minute, with a standard deviation of 41. Two children convalescent from glomerulonephritis were used as controls.

In a second paper, Emerson and Dole [19] reported values for glomerular filtration of 150 to 322 cc. per minute and a higher clearance of iodopyracet than normal for 4 nephrotic children having supernormal urea clearance. They concluded that high glomerular filtration rates in these children were due to an increased effective renal blood flow.

Comparable results were reported later on by Rubin, Rapoport and Randall[16] who used mannitol and sodium para-aminohippurate. No

TABLE 7.—*Tubular Reabsorption in Normal Children and in Children with Renal Disorders*

Tests	Normal	Nephrosis	Nephro-nephritis	Nephritis
Glomerular filtration rate (Cin), cc./min.	133	132.6	61.2	58.8
Tubular reabsorption of glucose (TmG), mg./min.	543	577.3	....	331.6
Tubular reabsorption of chlorides (TCl), mg./min.	531	569.6	479.7	323.4
TmG/Cin *	4.35	4.94	....	4.22
TCl/Cin *	3.96	4.96	5.60	3.72
TmG/TCl *	1.07	1.00	....	1.65
Cin/urea clearance *	1.82	2.10	2.42	1.90
Per cent (Cin-V)	96.6	98.7	97.7	95.9

Glomerular Filtration and Tubular Reabsorption Both in and Out of Edematous Stage of Nephrosis

	Edema	No Edema
(Cin), cc./min.	133	136.8
(TmG), mg./min.	578.4	595.9
(TCl), mg./min.	548.0	589.4
TmG/Cin *	4.74	4.47
TCl/Cin *	5.48	4.62
TmG/TCl *	1.19	1.06
Cin/urea clearance *	1.85	2.18

* Mean values of ratios calculated from individual ratios.

tubular reabsorption tests were performed for any of these patients, but from the determinations performed it was inferred that oliguria in nephrosis is due not to a low glomerular filtration rate but probably to an increased tubular reabsorption of water and a lessened extension electrolytes.

It is important to bear in mind that the moment in the evolution of nephrosis and nephritis when these tests are performed is an important factor in the expected results, as they will differ greatly according to pathologic and physiopathologic changes in the kidneys. Slight differences, however, were observed in a comparative study of results of tests both in and out of the edematous stage of nephrosis (table 7). Lower values for glomerular filtration rate and tubular

19. Emerson, K., Jr., and Dole, V.: Diodrast and Inulin Clearances in Nephrotic Children with Supernormal Urea Clearances, J. Clin. Investigation **22**:447 (May) 1943.

reabsorptive capacities for glucose and chlorides and higher tubular reabsorption of urea were observed during the edematous and oliguric stage of nephrosis. These results are secondary to oliguria, as was

TABLE 8.—*Summary of Data Obtained in Studies of Normal Children and Children with Renal Disorders*

Tests	M	± PEm *	σ	C
Normal				
Cin, cc./min. †	133 ‡	1.35	14.9	11.2
TmG, mg./min.	543	22.36	128.5	23.6
TmCl, mg./min.	531	15.49	89.0	16.7
Cd,§ cc./min.	695	41.13	183.0	26.3
TmD, mg./min.	53	3.70	11.0	20.7
Urea, cc./min.	76	2.89	16.0	21.0
Creatinine, mg./100 cc.	138	2.96	4.4	3.2
Cin/urea clearance	1.82	0.09	0.5	30.2
Creatinine/Cin	1.22	0.13	0.2	16.3
Cin/Cd	0.19	0.004	0.02	10.5
Cin/TmD	3.01	0.21	0.64	21.2
Cd/TmD	15.26	2.12	6.4	42.3
TmG/Cin	4.35	0.21	1.1	27.3
TmCl/Cin	3.96	0.16	0.9	24.7
TmG/TmCl	1.07	0.07	0.4	38.5
Nephrosis				
Cin, cc./min.	132.6	3.37	47.3	35.6
TmG, mg./min.	577.3	14.60	164.1	28.4
TmCl, mg./min.	569.6	16.20	161.3	28.3
Cd, cc./min.	793.2	35.7	183.3	26.6
TmD, mg./min.	57.3	3.3	17.0	29.6
Urea, cc./min.	66.9	1.9	18.7	27.9
Creatinine, mg./100 cc.	169.3	5.9	36.0	21.2
Cin/urea clearance	2.1	0.09	0.9	42.8
Creatinine /Cin	1.5	0.09	0.6	38.0
Cin/Cd	0.17	0.01	0.06	35.2
Cin/TmD	2.63	0.14	0.7	26.6
Cd/TmD	14.06	0.6	2.18	15.5
TmG/Cin	4.94	0.05	0.5	11.3
TmCl/Cin	4.96	0.12	1.2	24.5
TmG/TmCl	1.00	0.01	0.1	15.0
Nephronephritis				
Cin, cc./Min	61.2	4.64	37.5	61.2
TmG, mg./min.	....	....	....	....
TmCl, mg./min.	479.1	87.9?	226.0	47.1
Cd, cc./min.	316.2	16.0	33.5	10.5
TmD, mg./min.	2.0	....	....	....
Urea, cc./min.	36.8	3.4	14.2	38.5
Cin/urea clearance	2.42	0.29	1.1	43.8
Cin/TmD	0.15	0.43	1.3	20.0
TmCl/Cin	5.60	0.49	1.2	23.0
Glomerulonephritis				
Cin, cc./min.	58.8	3.64	32.9	55.9
TmG, mg./min.	331.6	39.30	142.6	43.0
TmCl, mg./min.	232.4	13.17	70.8	30.4
Cd, cc./min.	159.4	....	....	....
TmD, mg./min.	9.0	....	....	....
Urea, cc./min.	36.4	3.10	16.1	44.2
Creatinine, mg./100 cc.	....	....	....	....
Cin/urea clearance	1.9	0.07	0.4	21.0
TmG/Cin	4.22	0.32	1.2	28.4
TmCl/Cin	3.72	0.17	0.9	24.4
TmG/TmCl	1.65	0.10	0.3	17.5

* M indicates mean value; PEm, the probable error of the mean value, as corrected for small samples of TmG, TmCl, urea, Cin/urea, TmG/Cin, TmCl/Cin and TmG/TmCl; σ stands for standard deviation and C for coefficient of variation (Pearl, R.: Introduction to Medical Biometry and Statistics, ed. 3, Philadelphia, W. B. Saunders Company, 1940, pp. 349-359; Davenport, C. B., and Ekas, M. P.: Statistical Methods in Biology, Medicine and Psychology, ed. 4, New York, John Wiley & Sons, Inc., 1939, pp. 24-37).

† For explanation of symbols, see column 1, table 7.

§ Cd stands for iodopyracet clearance and TmD, tubular excretory capacity for iodopyracet.

‡ Computations were made according to number of determinations and not according to number of patients.

demonstrated by Shannon in the normal dog.[20] However, higher values for the ratios of tubular reabsorptive capacities for glucose and chlorides to the glomerular filtration rate were determined in same circumstances.[21]

This interpretation of an abnormally increased tubular reabsorption applied to the complicated pathogenesis of nephrotic edema does not exclude the extrarenal influence of hypoproteinemia and other probable factors. On the other hand, it indicates participation of the kidney and excludes the hypothesis of extrarenal origin of oliguria (decreased glomerular filtration rate secondary to escape of water and electrolytes to interstitial spaces on account of a decreased oncotic pressure). Theoretically hypoproteinemia should increase the glomerular filtration rate by the mechanism through which it allows deposition of edema. Thus, increased tubular reabsorption would be a substantial difference between nephrotic edema and edema due to simple depletion of plasma protein (nutritional and plasmapheretic edema) [6] and it would offer some explanation for the frequent failure of intravenousy administered protein therapy in the former type of edema.

Hypersthenuric oliguria (increased tubular reabsorption) in nephrosis, in which degenerative changes of tubular epithelium are the fundamental histologic alterations, would be in sharp contrast with hyposthenuric polyuria or pseudonormaluria (decreased tubular reabsorption) in the atrophic epithelium of chronic glomerulonephritis. One or more unknown factors determining or acting on the permeability of tubular epithelium could account for the alternating edematous and nonedematous characteristics of nephrosis. Impairment of renal circulation in mixed types of nephrosis would contribute to the formation of edema as in acute hemorrhagic nephritis.

Unfortunately, this subject is open to much scientific speculation and criticism. Further investigations and new therapeutic procedures will support or modify the concepts derived from the application of new clearance and saturation tests to the diseased kidney of children.

SUMMARY AND CONCLUSION

Clinical and pathologic observations on 84 patients with nephrosis studied at the Children's Hospital, Habana, Cuba, in the last ten years are reported.

20. Shannon, J. A.: Excretion of Inulin and Creatinine at Low Urine Flows by Normal Dogs, Am. J. Physiol. **114**:362 (Jan.) 1936.

21. The significant difference between means was measured by the formula $\sqrt{Pe_{m1}^2 + Pe_{m2}^2}$ and by Pearl's coefficient of group divergence (Introduction to Medical Biometry and Statistics, ed. 3, Philadelphia, W. B. Saunders Company, 1940, pp. 294 and 398-404). The coefficient of group divergence showed statistical difference for absolute values of the glomerular filtration rate, tubular reabsorptive capacities for glucose and chlorides and urea clearance in patients with nephritis and nephronephritis and of the ratios of tubular reabsorptive capacities for glucose and chlorides to the glomerular filtration rate in patients with nephrosis and nephronephritis as compared with normal children.

Frequency of nephritic symptoms was demonstrated by repeated Addis counts of urinary sediment, by biopsy specimens and by postmortem observations. In contrast to high incidence of inflammatory changes in nephrosis, only 4 patients showed the clinical picture of chronic glomerulonephritis. Importance of bacterial infection in the causation, pathogenesis and mortality rate of nephrosis is emphasized. Cutaneous infection is the second leading etiologic factor in nephrosis in Cuba. Salmonella and Shigella infections are also of etiologic importance as complicating factors in nephrosis as they too are common in Cuba. Mortality rate from infection was reduced from 25.5 to 13.5 per cent after introduction of sulfonamide drugs and antibiotic substances.

Participation of extrarenal factors in the pathogenesis of nephrosis could not be demonstrated. Involvement of kidneys, on the other hand, was demonstrated in every patient by clinical, functional and pathologic examinations. Albuminuria and hypoproteinemia could not be accepted as the only responsible factors in the pathogenesis of nephrotic edema. Actual albuminuria, according to daily diuresis, was not as high as the protein concentration in the urine. In a total of 469 determinations, the average concentration was 8.31 Gm., but the actual albuminuria was 2.02 Gm. per day. Salt intake during periods of active nephrosis caused deposition of edema and increase in albuminuria.

A higher concentration of cholesterol was observed in the renal venous blood of 2 nephrotic children as compared with concentrations determined simultaneously in the peripheral venous and arterial blood.

In a total of 165 clearance and saturation tests performed for 5 patients with acute hemorrhagic nephritis and 14 with nephrosis, results were as follows: in acute hemorrhagic nephritis effective renal plasma flow, glomerular filtration rate and tubular excretory and reabsorptive capacity were decreased. In nephronephritis or nephrosis with glomerular involvement the same results were obtained, but with a relative increase of tubular reabsorption. In uncomplicated nephrosis values for all these determinations were normal or increased. According to ratios of maximal tubular reabsorptive capacities for glucose and chlorides to the glomerular filtration rate, the ratio of glomerular filtration rate to urea clearance and the per cent of (Cin-V), a relative increase in tubular reabsorption was observed in nephrosis and a decrease in glomerulonephritis.

Increased tubular reabsorption is stressed as a renal factor in the still not well known pathogenesis of nephrotic edema.

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SEVERE ERYTHROBLASTOSIS FETALIS AND ICTERUS PRECOX

Occurrence of Both Diseases in the Same Family

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SINCE the literature is replete with evidence attesting to the etiologic role of the Rh factor in the pathogenesis of erythroblastosis fetalis in 90 per cent of the cases, it seems needless in this paper to dilate further on this subject. It is not generally recognized, however, that the A and B factors may also cause erythroblastosis fetalis,[1] cases of which Halbrecht[2] designated as icterus precox. In the case that will be reported here sensitization to the B factor was responsible for icterus precox three times in the same family. Moreover, the woman in question also had 2 full term babies with icterus gravis, both of whom died within three days, in spite of transfusions.

REPORT OF CASES

E. B., a quintipara, was referred to me because she had lost the second and fourth babies with icterus gravis, while the first, third and fifth babies survived. She was now pregnant for the sixth time and was greatly concerned about the outcome of this pregnancy.

Complete grouping and Rh-Hr tests on the woman and her family gave the results presented in table 1.

Anti-Rh antibody titrations on the mother's blood done by me with the agglutination method gave negative results, while the results of the plasma-conglutination method were positive, 128 units. For confirmation of my observa-

1. Polayes, S. H.: Erythroblastosis Fetalis in Mothers with Rh-Positive Blood: Report of Six Cases, with Comment on Isoimmunization with "A" and "B" Agglutinogens, Am. J. Dis. Child. **69**:99 (Feb.) 1945.

2. Halbrecht, I.: Role of Hemoagglutinins Anti-A and Anti-B in Pathogenesis of Jaundice of the Newborn (Icterus Neonatorum Precox), Am. J. Dis. Child. **69**:248 (Oct.) 1944.

TABLE 1.—*Results of Blood Grouping Tests on E. B. and Her Family*

TABLE 1.—*Results of Blood Grouping Tests on E. B. and Her Family*

Blood of	Group	Rh-Hr Type (Phenotype)	Genotype *
Mother	O	rh'rh	$r'r$
Father	B	Rh_2	R^2r
1st child (boy, aged 6½)	O	Rh_2	R^2r
3d child (girl, aged 3½)	B	rh'rh	$r'r$
5th child (girl, aged 1½)	B	rh'rh	$r'r$

*The genotypes are derived from the setup of the phenotypes in the family. Thus, the type Rh_2 child (the first child) can belong only to genotype R^2r, proving that the father is carrying an R^2 gene and the mother an r gene. Similarly, the 2 type rh'rh children can belong only to genotype $r'r$, of which the r' gene must have come from the mother and r gene from the father. Therefore, of the five possible genotypes for type Rh_2 persons, the father can only belong to genotype R^2r. Incidentally, this family again illustrates the application of Wiener's theory of inheritance of the Rh types and his nomenclature (see table 2), which keeps phenotypes and genotypes separate, a plan which the nomenclatures suggested by later workers do not follow.

TABLE 2.—*Classification of Rh Blood Types and Subtypes* *

TABLE 1.—*Results of Blood Grouping Tests on E. B. and Her Family*

Rh Blood Types	Reaction with Serum: Anti-Rh′	Anti-Rh″	Anti-Rh_0	Genotypes	Reaction with Serum: Anti-Hr′	Anti-Hr″	Rh Sub-types	Approximate Distribution (Percentage Among Caucasians in New York City)	
rh	Neg.	Neg.	Neg.	$r'r$	Pos.	Pos.	.....	13.0	
Rh′	Pos.	Neg.	Neg.	$R'R'$	Neg.	Pos.	Rh′Rh′	.01	1.0
				$R'r$	Pos.	Pos.	Rh′rh	1.0	
Rh″	Neg.	Pos.	Neg.	$R''R''$	Pos.	Neg.	Rh″Rh″	.005	0.5
				$R''r$	Pos.	Pos.	Rh″rh	0.5	
Rh′Rh″	Pos.	Pos.	Neg.	$R'R''$	Pos.	Pos.	.....	.01	
Rh_0	Neg.	Neg.	Pos.	r^0r^0	Pos.	Pos.	.....	2.0	
				r^0r					
Rh_1 (Rh_0′)	Pos.	Neg.	Pos.	R^1R^1	Neg.	Pos.	Rh^1Rh_1	20.0	54.0
				R^1R'					
				R^1r	Pos.	Pos.	Rh_1rh	34.0	
				R^1r^0					
				$R'r^0$					
Rh_2 (Rh_0″)	Neg.	Pos.	Pos.	R^2R^2	Pos.	Neg.	Rh_2Rh_2	3.0	15.0
				R^2R''					
				R^2r	Pos.	Pos.	Rh_2rh	12.0	
				R^2r^0					
				$R''r^0$					
Rh_1 Rh_2	Pos.	Pos.	Pos.	R^1R^2	Pos.	Pos.	.....	14.5	
				$R'R^2$					
				R^1R''					

* From Wiener, A. S.; Sonn-Gordon, E. B. S. and Handman, L.: *J. Immunol.* **57**: 203 (Nov.) 1947.

tions, I sent a sample of the woman's blood to Dr. A. S. Wiener, who obtained the following results:

Antibody	Method	Result
Anti-Rh	Agglutination	Negative
	Plasma-conglutination	Positive, 24 units
	Albumin-plasma conglutination [3]	Positive, 144 units
	Blocking test	Positive, ½ unit
Anti-A	Agglutination	3 units
	Plasma-conglutination	10 units
Anti-B	Agglutination	24 units
	Plasma-conglutination	64 units

It can be readily seen from these findings that the woman was strongly sensitized to the Rh factor and mildly sensitized to the B factor. However, since the father was heterozygous, it was difficult to determine whether the present fetus was Rh positive or Rh negative, and interference with the pregnancy was deemed inadvisable.

Two weeks later, antibody titrations by Dr. Wiener on the mother's blood showed the following results:

Antibody	Method	Result
Anti-Rh	Agglutination	Negative
	Albumin-plasma	Positive, 42 units
	Blocking test	Positive, 1½ units

Since the titer was not significantly higher and the baby was alive and active, it was decided to let the pregnancy go on until September 11, when labor was induced by rupturing the membranes ten days before term. Within twelve hours a live baby was delivered and examination of the blood of the baby revealed 5,600,000 red blood cells per cubic millimeter. The hemoglobin concentration was 140 per cent (20 Gm.). White blood cells numbered 19,400 per cubic millimeter, with 26 polymorphonuclear leukocytes, 1 stab form, 68 lymphocytes, 2 monocytes, 1 myelocyte, 2 eosinophils and 15 normoblasts, per hundred white blood cells. Polychromasia and macrocytes (2 plus) were present. The baby proved to be group B type rh, and so there was no indication for an exchange transfusion. The following morning the baby showed mild cyanosis but no jaundice. Ten cubic centimeters of group A and B substances was given intravenously as suggested by Wiener and Sonn [4] for treatment of such cases. The blood count that morning was as follows: There were 4,000,000 red blood cells per cubic millimeter; hemoglobin concentration was 98 per cent (14 Gm.). White blood cells totaled 19,100 per cubic centimeter with 54 polymorphonuclear leukocytes, 5 stab forms, 35 lymphocytes, 5 monocytes, 1 eosinophil and 2 normoblasts per hundred white blood cells.

Within thirty-six hours after birth mild icterus appeared which became more pronounced on the fifth day but gradually faded out and disappeared on the seventh day.

The red blood cell count and hemoglobin level remained at about 4,000,000 and 98 per cent (14 Gm.), respectively, for six days. On the eighth day the red cells numbered 4,900,000 and the hemoglobin concentration was 116 per cent (16.7 Gm.).

Antibody titrations on the infant's cord serum, performed by Dr. A. S. Wiener, gave the following results:

Antibody	Method	Result
Anti-Rh	Agglutination	Negative
	Albumin-plasma conglutination	Positive, 48 units
Anti-A	Agglutination	½ unit
	Plasma-conglutination	6 units
Anti-B	Both methods	Negative

Cord serum revealed an icterus index of 10 units by the acetone method.

Antibody titrations on the mother's blood at delivery showed the following results:

Antibody	Method	Result
Anti-Rh	Agglutination	Negative
	Albumin-plasma conglutination	Positive, 44 units
Anti-A	Agglutination	7 units
	Plasma-conglutination	6 units
Anti-B	Agglutination	24 units
	Plasma-conglutination	48 units

3. Wiener, A. S., and Hurst, J. G.: A New Sensitivity Test (Direct Test) for Rh Blocking Antibodies, Exper. Med. & Surg. **5**:285 (May-Aug.) 1947.

4. Wiener, A. S., and Sonn, E. B.: Permeability of the Human Placenta to Isoantibodies, J. Lab. & Clin. Med. **31**:1020 (Sept.) 1946.

These results show that the mother was sensitized to the B factor, as well as to the Rh factor, and that the anti-Rh antibodies of the mother had been transferred to the baby in a high titer. However, since the baby was Rh negative, the anti-Rh antibodies had no effect on the baby's blood, while the anti-B antibodies produced mild anemia and icterus, from which the baby recovered spontaneously. When the mother was questioned about the other babies (no. 3 and 5), she said their jaundice was deeper than the present baby's and that this baby thrived better. This may perhaps be attributed to the administration of the group A and B substances which the older children did not get.

COMMENT

This woman was an rh′ person; nevertheless, she begot 2 children with fatal erythroblastosis fetalis. This further proves the importance of considering an rh′ and rh″ woman as equivalent to being Rh negative, since these persons can become sensitized to the Rh_0 factor, as shown in this case.

From the setup of the phenotypes in the family, it was possible to derive the genotypes, and, since the father could belong only to genotype R^2r, one could easily conclude that he was heterozygous. A mating of R^2r with r′r can yield an equal number of offspring belonging to phenotypes Rh_2, Rh_1Rh_2, rh′ and rh.

It is worthy of note that an Rh-negative mother sensitized to the Rh factor can carry a high antibody titer for a long time. (This woman had an Rh-positive baby about three years prior to the present pregnancy.) This fact should be borne in mind, moreover, when contemplating the interruption of a pregnancy, since the baby in question may be Rh negative, as it proved to be in this case.

This case illustrates the importance of not ignoring the possibility of sensitization to the A and B factors in arriving at a diagnosis of erythroblastosis fetalis. These cases, known as icterus precox, are usually mild and tend to spontaneous recovery. I have had to give some of these babies one or more transfusions of 80 cc. of blood but all have recovered. It is believed that the administration of the A and B group substances has a favorable influence on the course of these cases.

This is an unusual case, because in the same family 2 persons with fatal icterus gravis and 3 with mild icterus precox were encountered.

SUMMARY

An unusual case is described in which a group 0 type rh′ mother had 2 babies with fatal erythroblastosis fetalis due to Rh sensitization, and 3 children of types rh′ and rh with icterus precox due to B sensitization.

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PREVALENCE AND DISTRIBUTION OF OSSIFICATION CENTERS IN THE NEWBORN INFANT

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IN TWO previous studies [1] it has conclusively been demonstrated that race and sex are of the utmost importance in an appraisal of the osseous pattern of newborn infants. These studies were based on the presence or absence of the center for the cuboid bone. They revealed that this center was found to be present more frequently in Negro than in white infants of the same sex. In both races the center for the cuboid bone was found to be present more frequently in female than in male infants.

It is the purpose of this report to complete the observations for the presence or absence of each of the nine other centers of ossification which may be visible in roentgenograms in the newborn infant, the weight at birth, race and sex being taken into consideration.

MATERIAL FOR STUDY

The material analyzed in the paper is the same as that used in the previous reports, in which only the center for the cuboid bone was studied.[1]

A total of 1,112 newborn infants (298 white boys, 267 white girls, 271 Negro boys and 276 Negro girls) were observed. These infants were live born to women admitted to the obstetric wards of the Johns Hopkins Hospital from May to June 1937 and from May to December 1938. No multiple births or syphilitic infants were included, and all infants were in sufficiently good physical condition to warrant a roentgenologic examination of their long bones within seventy-two hours of birth. These infants comprise somewhat more than one half of all the single-born infants admitted to the nursery during the periods covered in this study.

The infants were unselected except in terms of socioeconomic status, all the mothers being admitted to the ward service of the hospital. All infants under the care of private physicians were eliminated from the study. Furthermore,

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The data on which this study is based were collected by the Children's Bureau at a time when I was a member of their research staff. The presentation of the material is my own.

1. (*a*) Dunham, E. C.; Jenss, R. M., and Christie, A.; A Consideration of Race and Sex in Relation to Growth and Development of Infants, J. Pediat. **14**:156-160 (Feb.) 1939. (*b*) Christie, A.; Dunham, E.; Jenss, R. M., and Dipple, A. L.: Development of the Center for the Cuboid Bone in Newborn Infants: A Roentgenographic Study, Am. J. Dis. Child. **61**:471-482 (March) 1941.

only those multiparas were admitted to the obstetric service who had complications of pregnancy or some other condition which made them poor obstetric risks. All primiparas who applied for care were admitted to the wards for delivery.

Each infant was weighed within twelve hours after birth.

Roentgenograms were taken within seventy-two hours after birth and were read for the presence or absence of centers in the calcaneus, talus, cuboid bone, third cuneiform bone, distal epiphysis of the femur, proximal epihysis of the tibia, capitatum (or magnum), hamate bone (unciform bone), head of the humerus and head of the femur.

It is obvious that a study of the presence of a center in the neonatal period fails to furnish data with regard to the time that the center appears. It is likewise obvious that its size or area would also permit further differentiation, but this could not be realized because the technics are not practical for the measurement of these small centers in mass studies. Furthermore, the error in measurement is relatively large as compared with the physiologic variation inherent in the size of the center.

The data for the presence of these centers were analyzed in relation to birth, weight, sex and race. The results are shown in the accompanying table.

RESULTS

The table represents a complete study of the presence of centers of ossification as seen in roentgenograms in 1,112 newborn infants. The ten centers of ossification studied are listed in vertical columns in the table, and the six weight groupings are listed horizontally. The material was then analyzed for the presence of each center according to race and sex, that is for white boys, white girls, Negro boys and Negro girls.

It can be seen from a study of the table that in all (100 per cent) of the infants in each weight group the center for the calcaneus was present.

For the talus, in 72.7 per cent of the white boys who weighed less than 2,000 Gm., the center was present. In 83.3 per cent of the white girls this center was present, whereas in 90.9 per cent of the Negro boys and in 100 per cent of the Negro girls who weighed less than 2,000 Gm. this center was already present. In all the groups with the greater weight, 2,000 to 4,000 Gm. or more, except for 1 infant in the 3,000 to 3,499 Gm. group, the talus center was present.

For purposes of statistical evaluation, the presence of the center for the cuboid bone in relation to weight, sex and race, as well as length of period of gestation, age of mother, complication of pregnancy and parity, has been completely studied and reported.[1b] This center was selected because in general it was present in the newborn as many times as it was absent.

For purposes of future studies relating to fetal maturity, the centers of the distal epiphysis of the femur and the proximal epiphysis of the tibia are of the greatest clinical importance, since it has long been

Girls, 271 Negro Boys and 278 Negro Girls—Distributed According to Race, Sex and Weight at Birth.

Center of Ossification	Roentgenograms in Which Presence of Center was Clear, for Various Weight Groups (Gm.)											
	Less Than 2,000		2,000 to 2,499		2,500 to 2,999		3,000 to 3,499		3,500 to 3,999		4,000 or more	
	Total Number	Per-centage	Total Number	Per-centage	Total Number	Per-centage	Total Number	Per-centage	Total Number	Per-centage	Total Number	Per-centage
Calcaneous												
White boys	11	100.0	15	100.0	34	100.0	113	100.0	88	100.0	35	100.0
White girls	6	100.0	24	100.0	49	100.0	111	100.0	54	100.0	21	100.0
Negro boys	11	100.0	26	100.0	75	100.0	100	100.0	45	100.0	14	100.0
Negro girls	14	100.0	32	100.0	103	100.0	101	100.0	22	100.0	4	100.0
Talus												
White boys	11	72.7	15	100.0	34	100.0	113	99.1	88	100.0	35	100.0
White girls	6	83.3	24	100.0	49	100.0	111	100.0	54	100.0	21	100.0
Negro boys	11	90.9	26	100.0	75	100.0	100	100.0	45	100.0	14	100.0
Negro girls	14	100.0	32	100.0	103	100.0	101	100.0	22	100.0	4	100.0
Distal epiphysis of femur												
White boys	11	9.1	16	75.0	34	85.3	113	100.0	88	100.0	35	100.0
White girls	6	50.0	24	91.7	49	98.0	112	100.0	54	100.0	21	100.0
Negro boys	11	18.2	26	88.5	75	90.7	100	94.0	45	100.0	14	100.0
Negro girls	14	50.0	32	93.8	103	99.0	101	100.0	22	100.0	4	100.0
Proximal epiphysis of tibia												
White boys	11	0.0	16	18.8	34	52.9	113	78.8	88	84.1	35	97.1
White girls	6	0.0	24	54.2	49	75.5	112	85.7	54	90.7	21	90.5
Negro boys	11	0.0	26	38.5	75	62.7	100	76.0	45	80.0	14	92.9
Negro girls	14	14.3	32	40.6	103	76.7	101	88.1	22	86.4	4	100.0
Cuboid bone												
White boys	11	0.0	16	6.2	34	14.7	113	39.8	88	44.3	35	60.0
White girls	6	0.0	24	37.5	49	57.1	112	65.2	54	70.4	21	76.2
Negro boys	11	0.0	26	23.1	73	43.8	100	58.0	44	68.2	14	100.0
Negro girls	14	21.4	32	37.5	103	68.0	101	78.2	22	81.8	4	75.0
Head of humerus												
White boys	11	0.0	13	7.7	29	13.8	62	41.9	51	49.0	22	59.1
White girls	4	0.0	18	5.6	31	25.8	74	41.9	36	69.4	15	86.7
Negro boys	11	0.0	23	0.0	66	15.2	76	27.6	31	48.4	11	63.6
Negro girls	13	0.0	28	10.7	88	22.7	78	52.6	18	38.9	1	100.0
Capitate bone												
White boys	11	0.0	15	0.0	33	0.0	112	8.0	88	15.9	34	17.6
White girls	6	0.0	24	0.0	47	14.9	106	15.1	53	20.8	21	38.1
Negro boys	11	0.0	26	7.7	73	16.4	96	20.8	42	26.2	13	30.8
Negro girls	14	0.0	32	12.5	101	19.8	101	41.6	22	40.9	3	100.0
Hamate bone												
White boys	11	0.0	15	6.7	32	6.2	112	6.2	87	10.3	35	11.4
White girls	6	0.0	24	0.0	47	10.6	108	13.0	53	20.8	21	33.3
Negro boys	11	0.0	26	16.4	73	16.4	96	17.7	43	44.2	14	28.6
Negro girls	14	0.0	32	9.4	101	22.5	100	41.0	22	54.5	3	66.7
Third cuneiform bone												
White boys	11	0.0	16	0.0	34	0.0	113	2.7	88	2.3	33	3.0
White girls	6	0.0	24	0.0	49	0.0	111	0.0	54	5.6	21	9.5
Negro boys	11	0.0	26	3.8	74	8.1	100	15.0	43	14.0	14	14.3
Negro girls	14	0.0	32	6.2	103	13.6	101	16.8	22	18.2	4	25.0
Head of femur												
White boys	11	0.0	16	0.0	33	0.0	107	0.0	76	0.0	30	0.0
White girls	5	0.0	21	0.0	49	0.0	105	1.0	52	0.0	20	0.0
Negro boys	11	0.0	25	0.0	75	0.0	99	0.0	43	0.0	14	0.0
Negro girls	14	0.0	31	0.0	100	1.0	98	1.0	21	0.0	4	0.0

* These infants were born alive to mothers delivered in the ward service of the Johns Hopkins Hospital during parts of 1936, 1937 and 1938 and were examined roentgenographically within seventy-two hours of birth.

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known that the former appear six weeks before term, thus indicating physiologic maturity. In the groups with weight of less than 2,000 Gm., 9.1 per cent of the white boys and 50 per cent of the white girls already had the distal epiphysis of the femur. In the corresponding weight group, 18.2 per cent of the Negro boys and 50 per cent of the Negro girls had the distal epiphysis of the femur. In the 2,000 to 2,499 Gm. weight groups, 75 per cent of white boys and 91.7 per cent of white girls had the distal epiphysis of the femur, while in 88.5 per cent of Negro boys and in 93.8 per cent of Negro girls in this weight group, the distal epiphysis of the femur was present. In the 3,000 to 3,499 Gm. weight group, 85.3 per cent of white boys and 98 per cent of white girls had the distal epiphysis of the femur. In the same group, the center was present in 90.7 per cent of Negro boys and in 99 per cent of Negro girls.

In the weight group of less than 2,000 Gm., the center for the proximal epiphysis of the tibia was not present in any white boy, white girl or Negro boy, but was present in 14.3 per cent of the Negro girls. In the 2,000 to 2,499 Gm. group, 18.8 per cent of the white boys and 54.2 per cent of the white girls had the center for the proximal epiphysis of the tibia. Of the infants weighing 2,000 to 2,499 Gm., 38.5 per cent of Negro boys and 40.6 per cent of Negro girls had the center present. In the weight group of 2,500 to 2,999 Gm., 52.9 per cent of white boys and 75.5 per cent of white girls had the proximal epiphysis of the tibia present. In 62.7 per cent of Negro boys and in 76.7 per cent of Negro girls the center was present.

Further study of the table reveals several interesting points. For any selected center of ossification in infants of either race or sex, there is progressive prevalence as the weight at birth increases. In general, for each center of ossification in each of the weight groupings, greater prevalence was noted in the Negro girls than in the Negro boys and in the white girls than in the white boys, with several exceptions, such as the center for the head of the humerus, which was found in a higher proportion of white boys (7.7 per cent) than white girls (5.6 per cent). These discrepancies are undoubtedly due to sampling errors and do not disturb the validity of the obvious trend.

While the data presented apply to the right side only, the observation was made that asymmetry in the development of any given center is insignificant.

REVIEW OF THE LITERATURE

While as early as 1906 Pryor,[2] in this country, pointed out sex differences in the development of centers of ossification, his material and

2. Pryor, J. W.: Development of the Bones of the Hand as Shown by the X-Ray Method, Bull. State Coll. Kentucky, 1905, no. 5, series 2, pp. 1-5; Ossification of the Epiphyses of the Hand: X-Ray Method, ibid., 1906, no. 4, series 3.

method of study were limited. In 1921 Stettner [3] observed a small number of newborn infants and noted acceleration of osseous development in the female babies. In 1921 Adair and Scammon [4] studied the ossification centers for the wrist, knee and ankle in 100 newborn infants (45 girls and 55 boys). Only 4 of these infants were premature, and no mention was made of racial origin. Hess and Weinstock [5] were the first to point out the influence of both sex and race on osseous development, but these factors have not been appreciated generally. Their material was limited to a study of centers in the carpal bones.

The most frequently cited article on the subject is that of Menees and Holly [6] (1932). These investigators studied all centers of ossification which might be present at birth in 263 male and 237 female newborn infants. No infant under 2,000 Gm. was included, and no further weight divisions were used in analyzing their material. There were only 2 Negro infants in the entire series. Sex differences were noted indicating that the female infant was more advanced than the male. For the weight group of from 3,000 to 3,490 Gm., our results are in general agreement with the figures shown in the tables prepared by Menees and Holly.

Stuart,[7] in 1934, and Vogt and Vickers,[8] in 1938, studying material from the Center for Research in Child Health and Development at Harvard University, analyzed the osseous growth in development of 228 newborn infants (112 girls and 116 boys). The roentgenograms were taken within forty-eight hours after birth. The infants were not studied according to weight. As a matter of fact, the studies included no infants under 5 pounds (2,267 Gm.) in weight. The material was not studied according to racial groups.

Stampfel and Tscherne,[9] in 1939, reported roentgenographic studies on the long bones of 112 newborn infants (57 boys and 55 girls).

3. Stettner, E.: Ueber die Beziehungen der Ossification des Handskeletts zu Alter und Längenwachstum bei gesunden und kranken Kindern von der Geburt bis zur Pubertät, Arch. f. Kinderh. **68**:342-368 (Dec.) 1924.

4. Adair, F. L., and Scammon, R. E.: Ossification Centers of Wrist, Knee and Ankle at Birth, with Particular Reference to Physical Development and Maturity of Newborn, Am. J. Obst. & Gynec. **2**:35-60 (July) 1921.

5. Hess, A. F., and Weinstock, M.: A Comparison of the Evolution of Carpal Centers in White and Negro New-Born Infants, Am. J. Dis. Child. **29**:347-354 (March) 1925.

6. Menees, T. O., and Holly, L. E.: Ossification in Extremities of New-Born, Am. J. Roentgenol. **28**:389-390 (Sept.) 1932.

7. Stuart, H. C.: Standards of Physical Development for Reference in Clinical Appraisement: Suggestions for Their Presentation and Use, J. Pediat. **5**:194-209 (Aug.) 1934.

8. Vogt, E. C., and Vickers, V. S.: Osseous Growth and Development, Radiology **31**:441-444 (Oct.) 1938.

9. Stampfel, K., and Tscherne, E.: Die Röntgendiagnose der übertragenen Frucht, Ztschr. f. Geburtsh. u. Gynäk. **119**:31-44 (May) 1939.

These authors concluded that size rather than presence of the center alone was the index of maturity of the infant. No premature infants were included.

For completeness, the reader is also referred to the recent study of Kelly and Reynolds,[10] in which appearance and growth of ossification centers in white and in Negro infants were investigated. The birth weights of the infants are not given, and the material is not comparable to that in the present study.

COMMENT

Not only do these findings have research value, but the clinical implications are several. For a number of years it has been noted by clinicians that the 2,400 Gm. Negro female infant has greater physiologic maturity and ability to cope with extra uterine life than a white male infant of the same weight. Negro infants are physiologically more mature than white infants, and female infants of either race are more mature than male infants. This difference is borne out in mortality statistics.[11]

The accompanying table showing osseous development offers an explanation for these clinical observations. It is possible that the definition of prematurity should be revised with these observations in mind.

The accurate prediction of the weight of the fetus is of constant interest to the obstetrician. Maternal diabetes, toxemias at pregnancy, heart disease and chronic pulmonary diseases, as well as a history and clinical and laboratory findings indicating the possibility that the infant will be born with erythroblastosis fetalis, all raise the question of relative fetal maturity at the time of anticipated induction of labor or elective cesarean section for such a condition. Various technics of fetal encephalometry for predicting the weight of the fetus have been developed. With a thorough knowledge of the development of the osseous pattern in the newborn and with better technics for visualizing fetal parts, it is possible that much information can be gained *in utero* concerning the relative osseous (and physiologic) maturity of the infant.

From the purely investigative standpoint, it is clear that race and sex must be taken into consideration in studies on growth, in the evaluation of gain in weight during the neonatal period or in such studies as the evaluation of the efficacy of vitamin D in the prevention of rickets. Physiologically, clinically and from the standpoint of osseous

10. Kelly, H. J., and Reynolds, L.: Appearance and growth of Ossification Centers and Increases in the Body Dimensions of White and Negro Infants, Am. J. Roentgenol. **57**:477-516 (April) 1947.

11. Bakwin, H.: The Sex Factor in Infant Mortality, Human Biol. **1**:90-116 (Jan.) 1929.

development, Negro infants are quite different from white infants and the female infant differs from the male infant of the same weight level.

SUMMARY AND CONCLUSIONS

The patterns for development of the centers of ossification found in newborn infants are presented in tabular form. This study was based on 1,112 single-born newborn infants (298 white boys, 267 white girls, 271 Negro boys and 276 Negro girls). Their osseous development was studied according to weight at birth, sex and race. It would appear that the order of appearance of the centers is as follows: calcaneus, talus, distal epiphysis of the femur, proximal epiphysis of the tibia, cuboid bone, head of the humerus, capitatum, hamate bone, third cuneiform bone and head of the femur. In general, all centers were found to be farther advanced in infants who were judged to be more mature when weight at birth was used as the criterion. On the whole, the Negro infants had a greater prevalence of any one center than the white infants. In general, the female infants had a greater prevalence of each center than the male infants in both races in the various weight groups. The possible research and clinical significance of these findings is discussed.

Dr. Edwards A. Park, Dr. Nicholson J. Eastman and Dr. J. William Pierson, of the Johns Hopkins University School of Medicine; and Dr. Ethel Dunham and Dr. Katherine Bain, of the United States Children's Bureau, cooperated in making this study possible. Dr. A. Louis Dippel aided in the collection of the data, and Dr. Rachel M. Jenss assisted in the compilation and construction of the table.

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Case Reports

AGENESIS OF ABDOMINAL MUSCLES WITH ASSOCIATED MALFORMATION OF THE GENITOURINARY TRACT

A Clinical Syndrome

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THE CONGENITAL absence of the anterior and lateral abdominal musculature is a rare anomaly and perhaps would not merit additional description were it not for its simultaneous occurrence with certain malformations of the genitourinary tract. These malformations include an enlarged and hypertonic bladder, usually occupying an abdominal or fetal position, hydroureter, destruction or cystic degeneration of the renal parenchyma, with dilatation of the renal pelves and calyxes, and cryptorchism. A case with this combination of congenital anomalies is described in this paper.

REPORT OF A CASE

History.—A white boy 5½ months of age entered the pediatric service of the Mount Sinai Hospital on April 27, 1946 because of paroxysmal cough and wheezing respirations of four days' duration. The family history revealed no chronic, familial or degenerative disease. There were 4 siblings, each of whom was well and, except for congenital deafness in the next youngest child, normal. The patient was born at another hospital after an uncomplicated pregnancy. The period of gestation was forty weeks, and delivery was normal and spontaneous. The weight at birth was 8 pounds 1 ounce (3,666 Gm.); the length at birth was 21 inches (52.5 cm.). The Wassermann reaction of the maternal blood was negative. At birth the infant's abdomen was noted to be large and distended, and there appeared to be defects in the abdominal wall. The penis contained a large, pouchlike structure in which urine collected. A barium sulfate enema revealed no intestinal obstruction or dilatation. Three attempts at intravenous urography failed to demonstrate excretion of the dye. Examination of the urine showed a 1 plus reaction for albumin and many white blood cells. A dorsal slit of the foreskin was performed on the third day of the infant's life because of phimosis. He was discharged at the end of two months, still weighing 8 pounds (3,629 Gm.). While at home the infant was greatly constipated, requiring daily use of rectal suppositories to induce a bowel movement. The abdomen remained large and flabby. The weight increased gradually to 10 pounds (4,536 Gm.), but for the month prior to his admission, growth and development appeared stationary. Several days before his hospitalization, a cough with wheezing respirations developed. The appetite

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declined, and he vomited several feedings. The symptoms progressed, and he became listless and dehydrated.

Physical Examination.—The patient was a poorly developed, poorly nourished 5½ month old boy, pale and chronically ill in appearance, with a dry, irritating cough. The temperature was 98.6 F., the pulse rate 120 and the respiratory rate 28. He weighed 9 pounds 11 ounces (4,394 Gm.). The turgor of the skin was poor, and there appeared to be little subcutaneous fat. The fontanel was depressed, and slight cranial asymmetry was evident. The eyes were sunken, and the right ear drum membrane was mildly congested. The thoracic cage was narrowed and shortened, and the sternum inclined upward and forward. The lungs were resonant throughout; the breath sounds were unimpaired, and numerous coarse rales were audible bilaterally. The heart was normal. The abdomen was distended and protuberant and bulged noticeably in each flank when the child was in the recumbent position. The abdominal wall was very thin; the skin was thrown into many wrinkles and furrows, and muscular resistance to palpation was lacking. The lateral abdominal musculature appeared to be absent. Palpation over the recti abdominis gave the impression that these muscles were present, although considerably thinned. Muscular contraction was not visible on crying. The intestinal pattern was readily apparent beneath the skin, and hard fecal masses were palpable throughout. The liver extended 6 cm. below the costal margin. The spleen was firm and extended 4 cm. downward. The superficial veins over the abdomen and thorax were dilated. The kidneys were not palpable, and the bladder could not be made out. The testes were neither in the scrotum nor in the inguinal canals. On the ventral surface of the penis a large saclike structure began 1 cm. distal to the penile-scrotal junction and extended up to the corona. The structure was apparently connected with the penile urethra, as urine collected there and could be expressed by manual pressure. It was subsequently demonstrated that firm pressure above the pubis caused a flow of urine from the bladder into the penile pouch. The nails of the four lateral toes of the right foot were absent. Neurologic examination revealed no abnormality except the absence of the abdominal reflexes. Subsequently, when the abdominal distention was relieved, the skin became relaxed and appeared too large for its contained viscera; the folds and wrinkles became more prominent. The abdomen now gave a doughy sensation on palpation, and a firm, though vaguely outlined, mass could be felt above the pubis to the left of the midline.

Laboratory Examination.—The hemoglobin content of the blood was 42 per cent. There were 15,200 leukocytes per cubic millimeter, with 33 per cent neutrophils and 67 per cent lymphocytes. Urinalysis showed a specific gravity of 1.012, a 2 plus reaction for albumin and 15 to 20 white blood cells and 2 to 3 red blood cells per high power field. The total protein of the blood measured 6.8 Gm. per hundred cubic centimeters. The carbon dioxide-combining power of the blood was 39.3 volumes per cent. The urea nitrogen content of the blood was 28 mg. per hundred cubic centimeters. Escherichia coli and Pseudomonas aeruginosa were cultured from the urine on several occasions. Repeated blood cultures yielded no pathogens. The specific gravity of the urine remained consistently between 1.010 and 1.012, and albuminuria and pyuria were constantly present. The urea nitrogen level of the blood rose to 36 mg. per hundred cubic centimeters toward the end of the course of illness. The leukocyte count ranged from 9,000 to 22,000 cells per cubic millimeter, and, despite several blood transfusions, the hemoglobin concentration never rose higher than 74 per cent. A single determination of the blood pressure made during the third week of hospitalization was 80 mm. systolic and 40 mm. diastolic.

Course in the Hospital.—The patient was given 15,000 units of penicillin intramuscularly every three hours. Except for a rise in temperature to 105 F., attributed to a reaction to a blood transfusion on the second day in the hospital, the patient remained afebrile during the first week. He was listless; anorexia was profound, and he was given fluids, plasma and blood parenterally. Despite these measures, his weight fell rapidly to 8 pounds 12 ounces (3,969 Gm.). Because of the evidence of urinary infection and the repeated demonstration of Esch. coli as the offending organism, the patient was given 0.15 Gm. of sulfadiazine every four hours. On the eighth day in the hospital, the temperature rose to 103 F., and tonic and clonic convulsive seizures of all four extremities developed.

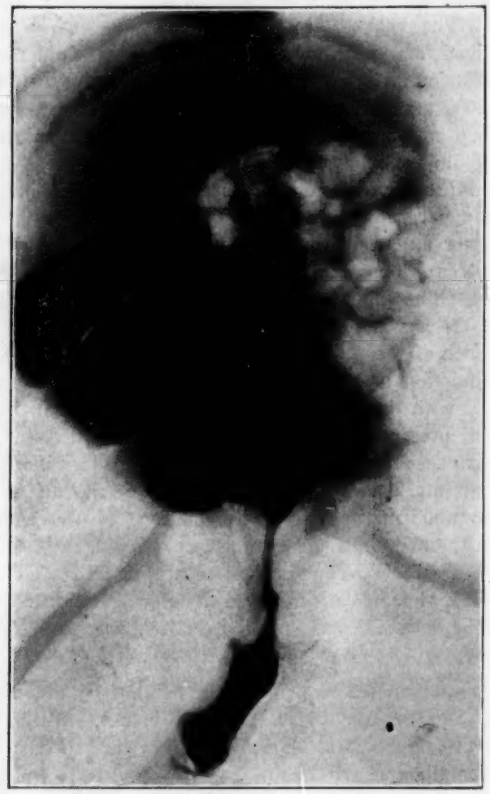

Fig. 1.—Retrograde cystogram showing the large, convoluted right ureter and bladder. The left ureter failed to visualize.

The fontanel was tense and bulging. Horizontal nystagmoid movements of the eyes and bilateral convergent strabismus were present. The patient assumed the opisthotonoid position. There was no frank nuchal rigidity, and the Kernig, Brudzinski, Chvostek and Trousseau signs were absent. Lumbar puncture released clear fluid, under increased pressure and containing an occasional red blood cell. The Pandy reaction was 4 plus. In the spinal fluid, sugar measured 90 mg., chlorides 702 mg. and protein 110 mg. per hundred cubic centimeters. Culture of the spinal fluid yielded no pathogens. Blood drawn for calcium and phosphorus determinations was unsuitable for study. Despite intravenous and oral admin-

istration of calcium, the patient exhibited tremors and convulsions intermittently for thirty-six hours. The highest temperature recorded during this episode was 106.4 F. The cause of the episode remained obscure until autopsy revealed thrombosis of the dural sinus.

Two roentgenograms of the chest failed to show any pathologic process in the lungs. A roentgenogram of the abdomen without the use of a contrast medium revealed a mass in the anterior portion of the pelvis, extending upward and displacing coils of intestine cephalad. This mass was interpreted as the bladder. It was deemed advisable to insert an indwelling catheter into the bladder to establish

Fig. 2.—Inner aspect of the abdominal wall at autopsy. Above the umbilicus are the well developed rectus abdominis muscles, and the large defect in the musculature is below.

continuous urinary drainage. The insertion of the catheter met with no resistance in the urethra or in the orifice of the bladder. A retrograde cystogram revealed an enlarged, dilated bladder and an enlarged, dilated and convoluted right ureter, resembling the large bowel in caliber.

The temperature continued to range from 100 to 105 F. during the remainder of the course of illness. The infant's condition declined steadily; the urinary output decreased, and he died on the twenty-first day in the hospital. The clinical cause of death was thought to be renal insufficiency and uremia.

Postmortem Examination.—The body was that of a poorly nourished, poorly developed boy. The thorax was thin and small. The abdomen was globular and enormously distended, with considerable bulging in the flanks. The umbilicus was everted. A saccular enlargement on the under surface of the penis extended from the base to the upper part of the glans. The urethral orifice was patent. The lateral four toes of the right foot were devoid of nails. Generalized wasting with little subcutaneous fat was apparent.

The abdominal wall was thin. The abdominal muscles, except the rectus abdominis, were poorly developed, consisting of only a few pale pink fibers. The

Fig. 3.—The genitourinary tract as seen at autopsy with the overlying viscera removed. The large, dilated megaloureters and the cystic, atretic left kidney can be distinguished. The testes are on each side of the abdominal cavity at the pelvic brim.

umbilical vessels and the urachus were obliterated. The abdomen contained 150 cc. of straw-colored fluid. The intestinal loops were distended. The right kidney was normal in position. The left kidney, greatly reduced in size, lay close to the midline. Both ureters were enormously dilated and tortuous, resembling the sigmoid colon. The bladder was dilated and hypertrophied, the fundus rising 4 cm. above the symphysis pubis. The testes lay at the upper border of the brim of the pelvis.

The heart and mediastinum showed no gross abnormalities. The lungs appeared heavier than normal, each weighing 110 Gm. The cut surface showed a congested, wet parenchyma, from which a moderate amount of pale, frothy fluid could be expressed. The liver was slightly enlarged and weighed 230 Gm. The parenchyma showed diffuse fatty infiltration. The gallbladder, the common bile duct, the cystic duct, the hepatic ducts and the portal vein and its tributaries were normal. The spleen appeared slightly enlarged, but the cut surface presented no abnormalities. The pancreas and adrenal, thyroid and parathyroid glands were grossly normal. Section through the sternum, ribs and vertebral bodies showed a pallid marrow.

The right kidney weighed 24 Gm. and measured 6.5 cm. in length. The capsule stripped with difficulty. The surface of the kidney was irregular, and many deep, fissure-like scars were evident. The intervening surface was smooth and had a strikingly mottled appearance. The cut surface showed a moist, swollen parenchyma. The corticomedullary demarcation was indistinct. Some of the calyxes were dilated, and all were lined with a dull gray mucosa. The ureter was enormously dilated and tortuous, measuring 3 cm. in diameter. The ureteral wall was thin and gray, and the lumen contained cloudy yellow urine. The ureter became narrowed at its junction with the bladder.

The left kidney was extremely small, measuring 3.5 cm. between poles. It was transformed into a mass of cysts with gray, transparent walls. Renal parenchyma could not be grossly recognized, and there was no pelvis. The ureteropelvic junction was a blind cul-de-sac. Below this level the ureter became wide and tortuous. Its wall was extremely thin. At a point 6 cm. below the kidney the lumen of the ureter was closed by a membrane. Between this point and its junction with the bladder, the ureter was a dilated, coiled structure with a thick, fibrous wall, the lumen of which contained a heavy, purulent material. The lower end of the ureter was completely closed off by a second membrane and did not communicate with the bladder. This block would explain the failure of the left ureter to be visualized on a retrograde cystogram.

The bladder was greatly dilated and thickened. The mucosa showed multiple pale, cystlike nodules. The ureteral orifices were normal. Valvelike folds were present distally on the posterior wall of the prostatic urethra. The prostatic tissue was not grossly identifiable. In the penile portion, the urethra became dilated, forming a large sac, which extended to the glans. The testes were grossly normal.

The brain and spinal cord appeared normal. The superior longitudinal and the right lateral sinuses contained several adherent thrombi. Both middle ears were normal.

Microscopic Examination.—The essential pathologic change was in the abdominal muscles and the genitourinary tract. The three layers of abdominal muscles were not fully developed. The internal oblique muscles were reduced to but a few fibers, widely spaced and extremely thin. In some sections the muscle was entirely absent. The external oblique and transversalis muscles were present but greatly reduced in thickness. The muscle fibers, when present, were normal in appearance. The thickness of the muscle layer lateral to the rectus abdominis muscles measured from 1 to 2 mm.

The wall of the bladder was thickened, and no elastic fibers were demonstrated. A low grade inflammatory reaction was present. The right ureter showed pronounced thickening of the wall, with round cell infiltration of the submucosa. The

left ureteral wall was fibrous in structure and in sections was devoid of epithelium. The right kidney showed subacute pyelonephritis with degenerative changes. The tubules were dilated and contained casts. The glomeruli were preserved, and a small amount of scarring was seen. The pelvis showed subacute inflammation and some fibrous thickening. The left kidney was small and polycystic, containing only a few abortive glomeruli and tubules. The cysts were probably dilated collecting tubules surrounded with abundant connective tissue.

The pathologic diagnosis was (1) agenesis of the abdominal muscles, (2) hypertrophy and dilatation of the bladder, (3) bilateral megaloureter, (4) hydronephrosis and pyelonephritis of the right kidney, (5) polycystic left kidney, (6) diverticulum of the urethra, (7) cryptorchism, (8) bronchopneumonia, (9) fatty infiltration of the liver and (10) organized thrombi in the superior longitudinal and right lateral dural sinuses.

COMMENT

Nearly 41 cases of agenesis of the abdominal musculature have been reported to date, and, despite its rare occurrence, the condition appears to be a definite clinical syndrome. The defect is readily apparent at birth or shortly thereafter, and the appearance of the infant in most cases is strikingly similar. The abdominal wall is exceedingly thin, the skin is thrown into many wrinkles and folds and appears too large for its contained viscera. The umbilicus is described frequently as a thin scar or a slitlike structure and is often lost in or obscured by the folds in the skin. There is usually considerable bulging of the flanks as the infant lies in the recumbent position. The superficial abdominal viscera are readily palpable. The muscular defect is variable, the muscles being totally absent in some of the infants or completely intact, but extremely thin, in others. Usually, the absence of abdominal muscles can be ascertained on physical examination. Crying as a rule fails to produce any visible muscular contraction, and electrical stimulation causes either a weak contraction or no contraction at all. The muscles most frequently present are the rectus muscles, and they are usually described as being present above the umbilicus but as fading or being entirely absent below. The external and internal oblique and the transversalis muscles are variably described as being completely absent, as showing only scattered fibers or bundles in their normal location or as being present only at their origin or insertion. Many of the patients showed accompanying thoracic deformities. Several infants, including the one whose case is reported here, assumed the position of opisthotonos, and this may be ascribed to absence of any countertraction to overcome the normal tonus of the sacrospinalis muscles. In 26 of the cases the urinary bladder was hypertrophied and extended above the pubis. In 16 cases one or both ureters were dilated. Pathologic changes in the kidneys, including dilatation of the pelves and calyxes and destruction of the parenchyma, occurred in 11 subjects. In 25 cases the testes were

intra-abdominal, while in the remainder no mention was made of their position. Only 1 [1] case of the anomaly occurred in a girl. Unfortunately, no autopsy was performed. A varus or valgus deformity was present in 6 cases. Death occurred before the age of 2 years in 30 cases and was attributed to intercurrent infection in most of them.

Obstructive uropathy, of either the organic or the neurogenic type, has been adequately described as a pathologic entity of infancy and childhood.[2] Autopsy in these cases nearly always reveals congenital obstruction of the urinary tract. In those cases in which a demonstrable obstructive lesion is evident, the abdominal wall is always intact. The reverse is true of those rare instances in which the particular syndrome under discussion occurs. In these cases, the pathologic changes in the genitourinary tract are qualitatively identical with those occurring in infravesicle obstruction, except that in the former a greater or lesser degree of agenesis of the abdominal musculature is present and no pathogenetic obstructive factor can, as a rule, be identified. In only 2 of the cases previously reported were any lesions of an obstructive nature described at autopsy. Housden [3] reported seeing a prominent longitudinal ridge projecting into the lumen from the anterior wall of the prostatic urethra. Despite this postmortem observation, urine was voided freely and a catheter was inserted easily during the life of the patient; it is difficult to imagine this lesion constituting the initiating force in the development of the advanced hydronephrosis. In Howard's case,[4] that of a newborn infant who died within several hours with pulmonary atelectasis, complete atresia of the urethra, with no anatomic patency, was seen.

Many theories have been advanced to explain the pathogenesis of this syndrome. Histologic examination of the spinal cord in 3 of the previously reported cases [5] and in the present case revealed no evidence

1. Hofstein, J.: Absence congénitale des muscles abdominaux chez un nouveau-né du sexe féminin, Gynéc. et obst. **22**:23, 1930.

2. Campbell, M.: Pediatric Urology, with a Section on Bright's Disease in Infancy and Childhood, New York, The Macmillan Company, 1937, vol. 1, p. 122.

3. Housden, L. G.: Congenital Absence of the Abdominal Muscles, Arch. Dis. Childhood **9**:219, 1934.

4. Howard, P. J.: Congenital Absence of the Abdominal Muscles and Genitourinary Malformation: Report of Two Cases, Am. J. Dis. Child. **60**:669 (Sept.) 1940.

5. (*a*) Garrod, A. E., and Davies, L. W.: On a Group of Associated Congenital Malformations, Including Almost Complete Absence of the Muscles of the Abdominal Wall, and Abnormalities of the Genito-Urinary Apparatus, Med.-Chir. Tr. **88**:363, 1905. (*b*) Hall, G.: Two Cases of Congenital Deficiency of the

(Footnote continued on next page)

of intrauterine disease. In Guthrie's case [6] the apex of the bladder was firmly adherent to the umbilical cicatrix; thus, the bladder could not contract maximally and empty itself completely. This condition led to urinary stasis and back pressure effects throughout the urinary tract. It is interesting to note that in 6 other cases the bladder was adherent to the umbilicus either directly or by a persistent urachus,[7] and that in another case it was bound to the anterior wall by a well defined mesentery.[8]

Bardeen, in discussing Osler's case, advanced two possible explanations.

1. The bladder, because of lack of resistance due to the weakness of the abdominal wall, fails to contract and to empty itself completely, and instead expands.

2. The vascular plexus derived from the internal mammary and the epigastric arteries, the formation of which normally precedes that of the abdominal muscles, may be deranged or its formation prevented in the embryo, and the growth of the abdominal muscles thereby impeded. The circulatory disturbances may also cause abnormalities of the bladder and ureters.[9]

Ikeda and Stoesser [7c] and Baxter [10] stated the opinion that the abdominal defect in their cases was due to the failure of embryonal skeletal muscle to extend forward into the anterior portion of the abdominal wall and that the hypertrophy of the bladder was a secondary manifestation.

Muscles of the Abdominal Wall Associated with Pathological Changes in the Genito-Urinary Organs, Lancet **2**:1672, 1907. (*c*) Lichtenstein, B. W.: Congenital Absence of Abdominal Musculature: Associated Changes in Genitourinary Tract and in Spinal Cord, Am. J. Dis. Child. **58**:339 (Aug.) 1939.

6. Guthrie, L.: Case of Congenital Deficiency of the Abdominal Muscles, Tr. Path. Soc. London **47**:139, 1896.

7. (*a*) Stumme, E. G.: Ueber die symmetrischen kongenitalen Bauchmuskeldefekte und über die Kombination derselben mit anderen Bildungsanomalien des Rumpfes (Hochstand, Hypertrophie und Dilatation der Blase, Ureterendilatation, Kryptorchismus, Furchennabel, Thoraxdeformität, etc.), Mitt. a. d. Grenzgeb. d. Med. u. Chir. **11**:548, 1903. (*b*) Thatcher, L.: Case of Congenital Defect of Abdominal Muscles with Anomaly of Urinary Apparatus, Edinburgh M. J. **11**:127, 1913. (*c*) Ikeda, K., and Stoesser, A. V.: Congenital Defect in the Musculature of the Abdominal Muscles: Case, Am. J. Dis. Child. **33**:286 (Feb.) 1927. (*d*) Housden.[8] (*e*) Garrod and Davies.[5a]

8. Moncrieff, A.: Specimen from a Case of Congenital Deficiency in Abdominal Muscles, Brit. J. Child. Dis. **28**:220, 1931.

9. Osler, W.: Congenital Absence of the Abdominal Muscles with Distended and Hypertrophied Urinary Bladder, Bull. Johns Hopkins Hosp. **12**:331, 1901.

10. Baxter, E. H.: Congenital Absence of Abdominal Muscles, Ohio State M. J. **28**:840, 1932.

Hall,[6b] in discussing the postmortem observations in the case previously reported by Bolton,[11] noted that the microscopic appearance of the muscle fibers still discernible in the abdominal wall favored the hypothesis of an anomaly of early developmental origin rather than that of atrophy subsequent to previous normal development. Later, Eckhoff[12] stated that, despite the general deficiency, the individual muscle fibers in his case were microscopically normal. A normal histologic structure was also demonstrated in the present case. Stunme[7a] explained the pathogenesis of the syndrome on the basis of a nonpersistent obstruction. He asserted that an occlusion of the urethra occurs late in fetal life, causing retention of urine, with resulting dilatation and hypertrophy of the bladder and ureters and the attendant changes in the kidneys. Pressure from these enlarging organs leads to atrophy

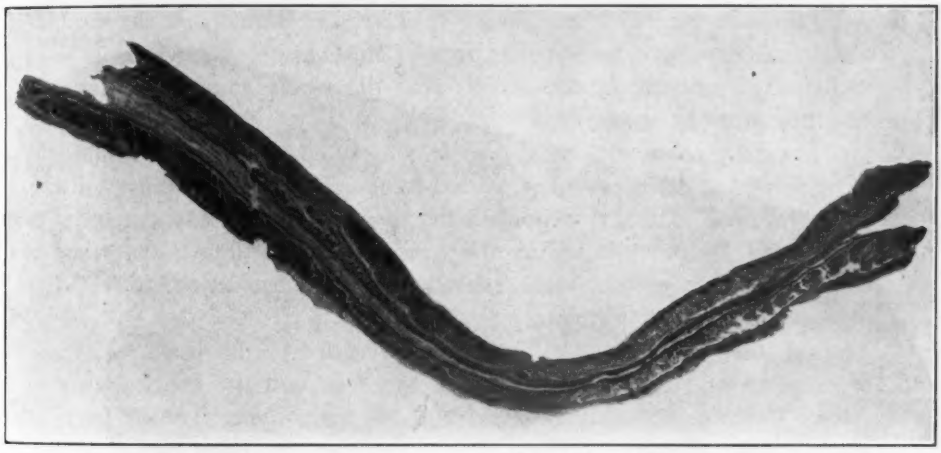

Fig. 4.—Photomicrograph of a cross section of the abdominal musculature, showing the extreme thinness of the layers of muscle.

of the lower segments of the rectus and the lateral abdominal muscles. In addition, pressure from these organs on the umbilical vessels decreases the blood supply and thereby decreases embryonic nutrition; interference with the returning circulation produces ascites, which is an additional increment to the intra-abdominal pressure. Cryptorchism occurs because of the failure of the testes to descend into the inguinal canals as a result of the mechanical blockage. He expressed the belief that the obstructive cause of urinary retention subsequently disappears. Thatcher[7b] concluded that the appearance of the abdomen in these patients suggested previously existing severe distention which disap-

11. Bolton, C.: Congenital Absence of Lateral Abdominal Muscles, with Enlargement of Bladder and Ureters, Tr. Clin. Soc. London **38**:247, 1905.

12. Eckhoff, N. L.: Case of Congenital Deficiency of Abdominal Musculature, Guy's Hosp. Rep. **73**:490, 1923.

peared before birth. The wrinkled appearance of the skin of the abdomen reported in many cases lends confirmation to this view.

Lichtenstein [5e] found two fundamental objections to Stumme's theory.

1. The exact nature of the obstruction is not stated.

2. In the cases of an obstructive uropathy secondary to an organic lesion the agenesis of the abdominal muscles is not present.

In Lichtenstein's case, abdominal muscle tissue was completely absent. He inclined to the view that this condition was a defect of development and not one of pressure atrophy or of fetal dystrophy. Lichtenstein's concept of the pathogenesis was based on a disturbance in the functional dynamics of the bladder. Normally, the bladder expels urine against resistance, for the pressure of the amniotic fluid is greater than atmospheric presure. The fetus, like the infant, uses contraction of the abdominal wall as an accessory mechanism of micturition to increase the intra-abdominal expulsive force. The lack of this accessory force leads to incomplete emptying of the bladder and the whole gamut of changes resulting from back pressure.

Howard [4] postulated that the pathologic changes in the bladder indicate that it functioned against a resistance; hence, the cause must be obstructive. He also expressed the opinion that the explanation of obstructive hydronephrosis in the presence of an intact abdominal musculature lay in the late appearance of the obstruction, after the muscles had already formed.

In a recent article, Daut, Emmett and Kennedy [13] described the case of a boy with typical changes in the abdomen and the genitourinary tract. Cystoscopic study revealed a moderately hypertrophied interureteric bar. Because, in their opinion, urinary retention occurs as a result of imbalance between the detrusor urinae muscle and the vesical neck, they performed a transurethral resection of the neck of the bladder. Eight and one-half months later there was no residual urine; the blood urea nitrogen level had fallen, although it was still abnormal, and the degree of pyuria had decreased. The authors stated their belief that changes in the urinary tract occur from obstruction of the neck of the bladder and that the obstruction is not always apparent until transurethral resection is attempted. They did not explain the muscular agenesis.

Until such time as the precise interrelations of embryonic development are worked out and the effects of the dynamics of the growth of one system on the rest of the growing embryo are established, it will not be possible to determine whether agenesis of the abdominal muscles

13. Daut, R. V.; Emmett, J. L., and Kennedy, R. L. J.: Congenital Absence of Abdominal Muscles with Urologic Complications, Proc. Staff Meet., Mayo Clin. **22**:1, 1947.

and the pathologic changes in the genitourinary tract represent the end results of a single functional defect or whether one is the cause of the other. Lacking such knowledge, one may argue that, since congenital obstructive hydronephrosis never causes muscular agenesis and since in the syndrome described in the present report no organic obstruction is observed, the muscular agenesis is the initiating force in the changes in the urinary tract and that the agenesis operates by causing incomplete emptying of the bladder, leading to the adynamic type of hydronephrosis.

CONCLUSIONS

A case of agenesis of the abdominal musculture and pathologic changes in the genitourinary tract is described. Several theories concerning the origin of the syndrome are presented.

Dr. Lotte Strauss described the postmortem examination.

Louisiana State University School of Medicine.

A BREAST AND BOTTLE SHY INFANT AT 21 YEARS OF AGE

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I HAVE received numerous inquiries as to the subsequent fate of the unusual case of the breast and bottle shy infant reported on in the AMERICAN JOURNAL OF DISEASES OF CHILDREN.[1] While she has never had a good appetite, her anorexia improved as she got older, and it is noteworthy that her appetite improved decidedly after an attack of whooping cough at the age of 9 years; the only other illness was chickenpox at 10. She began to talk at 10 months, to walk at one year and to feed herself at 2 years. She was able to make simple sentences very early. At the age of 2 she could repeat little stories by memory and knew when to turn the pages of a nursery book by the pictures.

Examination on Sept. 10, 1947, revealed an only child of an introvert type, who was inclined to be lazy. She was still particular as to the kind of food she ate but was not allergic to any foods. She was 21 years of age, 5 feet 6 inches (168 cm.) tall and weighed 135 pounds (61.2 Kg.). The body build was of a linear type. Fatigue posture was evident, although at the age of 15 the patient won a medal at a summer camp for good posture and swimming and was a junior life-saver. The head was of normal shape, with high forehead and narrow nose (tonsils and adenoids had been removed). She did not breathe through the mouth. The cheekbones were high with a somewhat receding lower jaw, thick lips and wide mouth. The eyes were normal. The thyroid showed slight adolescent enlargement. Normal breast development, round shoulders and winged scapulas were present. The heart and lungs were normal. Slight abdominal protuberance and a mild degree of lordosis were noted. The extremities were long, with no bowing of the legs.

Personality.—The patient had no special personality or behavior problems; she was highstrung and had a violent temper when crossed. She was clever and witty with a keen sense of humor, very popular with both sexes and held friends easily. She argued much with her mother and seemed to like her father better. Her speech was rapid but normal, and she used good diction and grammar. Her hearing was acute. She liked to collect letters, especially invitations. Her intelligence quotient was normal; she was not musically inclined. She made average grades in school without too much study. She had just finished a four year college course and entered a nursery teachers' training course for which profession she should be well qualified, since she gets along exceedingly well with children. She was a counselor and teacher of boating and swimming at

1. Feldstein, G. J.: A Breast and Bottle Shy Infant, Nursing only When Asleep, Am. J. Dis. Child. **35**:103 (Jan.) 1928.

a girls' summer camp this year. Her appetite was still only fairly good; she liked meats except chicken but disliked pastries or other rich foods.

In spite of the serious feeding difficulties of her early life, apparently on a neuropathic basis, this girl developed into an average young woman of 21 years

The breast and bottle shy infant at 12½ years of age.

of age. Her mental, physical and psychic development was not appreciably affected by her extreme breast and bottle shyness in infancy. If she marries and has children, it will be of interest to note whether this trait appears in any of her offspring.

Progress in Pediatrics

BCG VACCINATION AMONG MEDICAL AND NURSING STUDENTS

ERNEST E. IRONS, M.D.
CHICAGO

NURSING students at the Cook County Hospital, Chicago, have been vaccinated with BCG since 1940. Vaccination is administered during their first week of training. Only those students are vaccinated who do not react to 1 mg. of old tuberculin and who have normal roentgenograms of the chest. In none of the 142 nurses vaccinated over a seven year period has pulmonary tuberculosis developed. In 199 controls who did not react to 1 mg. of old tuberculin and who were less exposed to tuberculosis than the vaccinated nurses, since the latter are allowed to work in the tuberculosis hospital, whereas the former are not, there were 3 cases of pulmonary tuberculosis. All required rest in bed and 2 sanitarium care. Three additional cases of pulmonary tuberculosis occurred among the 286 positive reactors to tuberculin.

In the 109 medical students vaccinated at the University of Illinois since 1939, there have been no cases of pulmonary tuberculosis. In the nonvaccinated group, 4 cases have been reported. The complete data are not yet available because of the interruption of the war. Questionnaires are being sent out to obtain more recent information.

Abstract of a paper presented before the Chicago Medical Society, Nov. 14, 1947.

METHODS OF BCG PRODUCTION AND VACCINATION

SOL ROY ROSENTHAL, M.D., Ph.D.
CHICAGO

IN A REPORT by the United States Public Health Service,[1] as well as in one made for the British government,[2] it was agreed that BCG production should be carried out by a central laboratory. The reasons for this universal agreement were: (1) to afford a standard method of comparison; (2) to maintain the fastidiousness of the organism; (3) to guarantee the minute care necessary in production of the vaccine, as the final product is a living organism to which no preservative can be added, and (4) to insure accurate and careful determination of the virulence.

If such a program is followed, the results of vaccination in human subjects in various parts of the country can be readily correlated and the stability of the organisms assured.

HISTORIC ASPECTS

A review of the literature reveals that "accidents" have occurred when central laboratories well qualified to produce the vaccine were not established. In the Lübeck, Germany, disaster,[3] BCG was mixed with virulent cultures of tubercle bacilli which were kept in a common incubator. Two hundred and seventy-one children were infected with virulent tuberculosis and 77 died. In this country, the cultures were contaminated in the experiment in New York city[4] and lost in the Philadelphia laboratories.[5] Such calamities can be avoided by the

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A paper presented before the Chicago Pediatric Society, Oct. 14, 1947.

From the Tice Laboratories and Clinic of the City of Chicago Municipal Tuberculosis Sanitarium and the University of Illinois.

1. Report of a Conference on BCG Vaccination, Pub. Health Rep. **62:346**, 1947.

2. Tytler, W. H.: Memorandum on BCG for a Joint Committee of The Tuberculosis Association, The Joint Tuberculosis Council and The National Association for the Prevention of Tuberculosis, for the consideration of the Right Honourable Aneurin Bevan, Minister of Health, and the Right Honourable Joseph Westwood, Secretary of State for Scotland, Nov. 19, 1943, p. 5.

3. Lange, L., and Pescatore, H., in Arbeiten aus dem Reichsgesundheitsamte, Die Säuglingstuberkulose in Lübeck, Ministry of the Interior, Berlin, Julius Springer, 1935.

4. Levine, M. I.: An Evaluation of the Use of BCG in the Prevention of Tuberculosis in Infants and Children, Am. J. Pub. Health **37**:1089, 1947.

5. Personal communication to the author.

establishment of a central laboratory the sole function of which is the production and assay of BCG.

The organism was actually isolated in 1906 from the milk of a tuberculous cow, and in 1908 Calmette [6] and Guérin began their studies to reduce the virulence of this bovine bacillus. After approximately 230 transfers on bile-potato medium over a period of thirteen years, this organism, which originally produced progressive tuberculosis in animals, was so attenuated that only local tubercles were produced at the site of inoculation. Animals thus given injections resisted a virulent infection to a great extent. This was observed to be true in guinea pigs, rabbits, calves and, finally, monkeys. When Calmette and Guérin were assured that the organism would not produce progressive disease and that a certain degree of protection from virulent tubercle bacilli was afforded by this form of vaccination, they allowed Weill-Hallé and Turpin, of Paris, to vaccinate the first child in 1921.[7]

METHOD OF CULTURE

The method used at present in culturing the organism follows the dictates of the Pasteur Institute of Paris.[8] The organisms are grown on bile-potato medium and transferred on plain potato medium and then on Sauton's medium, a synthetic medium composed of amino acid (asparagine), glycerin and buffered salts. After two transfers on synthetic medium, the organisms are gathered for production of the vaccine. Fifteen milligrams of organism per cubic centimeter is used for the standard vaccine.

The mother culture of each batch of vaccine is injected into guinea pigs, half of which are killed one month after injection, at the time the vaccine is released, and the other half is allowed to live for one year. Guinea pigs are also inoculated with the vaccine itself and allowed to live for at least one year. At no time, with the use of thousands of guinea pigs and rabbits over a thirteen-year period, has progressive tuberculosis ever been noted in the animals given these injections. Sterility studies, as well as viability studies, are made on every batch of vaccine.

METHOD OF ADMINISTRATION

The method of administering the vaccine, when it was first given to human beings, was by mouth. It was soon learned that the percent-

6. Calmette, A.: La vaccination préventive contre la tuberculose par le B.C.G., Paris, Masson & Cie, 1927.

7. Weill-Hallé, B., and Turpin, R.: Premiers essais de vaccination antituberculeuse de l'enfant par le bacille Calmette-Guérin (BCG), Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1589, 1925.

8. Rosenthal, S. R.: Studies with BCG; Present Method of BCG Cultivation and Vaccine Production as Practiced at Pasteur Institute and Tice Laboratories, Am. Rev. Tuberc. **35**:678, 1937.

age of persons who became positive reactors to tuberculin following this method was low. The subcutaneous method was then introduced by Weill-Hallé but was discredited by the abscesses that were produced.[9] Wallgren introduced the intradermal method,[10] and, although it produced ulcers or abscesses, they drained easily to the exterior.

It can be readily understood that for a method of vaccination to become universally popular, complications must be at a minimum. For this reason, the Tice Laboratories developed the method of scarification by multiple puncture.[11] The technic of the method is as follows: A drop of vaccine is placed on the outer aspect of the arm after cleansing with alcohol. A sewing type needle, similar to the one used for vaccinia, is held between the thumb and the index finger about 1.5 cm. from the point. The thumb and needle should form a continuous line. With the shaft of the needle held tangentially to the skin, the vaccine is spread in linear fashion for a distance of 2.5 cm. By a downward pressure, exerted to a large extent by the thumb, the skin is pierced with the needle point through the vaccine. After this downstroke, which engages the point of the needle into the skin, an upward movement is exercised without disengaging the needle. The point of the needle remains buried in the skin on the upstroke. This precaution makes the method foolproof. The punctures are placed about 2 to 4 mm. apart and 10 punctures are made in a line. The vaccine is spread to a second line parallel to the first and 4 to 6 mm. away. Thus, three lines of 10 punctures each are made in an area of approximately 2.5 by 1.5 cm. The vaccine is allowed to dry on the arm; no blotting or covering with dressings is practiced. Wetting of the arm should be avoided for twenty-four hours.

The lesions following the multiple puncture method in newborn infants resemble goose flesh after two to six weeks following vaccination. The mother rarely knows which arm was inoculated. In children and adults each puncture progresses to form pink papules from pinhead to 3 mm. in size. These papules, after four to eight weeks, regress rapidly. The recipient is usually unaware of which arm was scarified. The draining lymph nodes may be palpable two weeks after vaccination, but never enlarge to the extent that the recipient is aware of it. Ulceration and breaking down of lymph nodes have never been seen.

By this method not only are complications practically nil, but the percentage of persons who react to tuberculin following vaccination is almost universal (99.7 per cent) after four to six weeks. The duration

9. Weill-Hallé, B.: La vaccination antituberculeuse par l'injection sous-cutanée de B.C.G., Presse méd. **36**:721, 1928.

10. Wallgren, A.: Intradermal Vaccinations with BCG Virus: Preliminary Note, J. A. M. A. **91**:1876 (Dec. 15) 1928.

11. Rosenthal, S. R.: The Multiple Puncture Method of BCG Vaccination, Am. Rev. Tuberc. **39**:128, 1939.

of the tuberculin reaction after a single vaccination is almost 80 per cent after six to six and one half years. This method has been adopted in France,[12] in Norway [13] and in some of the South American countries.[14]

SUMMARY

1. The recommendation for the establishment of a central laboratory for BCG production, as discussed by the United States Public Health Service and the Prophit Survey for the British government, is substantiated.

2. The method of culture and production of BCG vaccine is briefly described.

3. The scarification method by multiple puncture is considered the one of choice for the administration of the vaccine.

Hotel Del Prado (10).

12. Nègre, L., and Bretey, J.: Vaccination par le BCG par scarifications cutanées, Paris, Masson & Cie, 1942. Weill-Hallé, B., and Lagroua, M. A.: La vaccination contre la tuberculose par le BCG; méthode des scarifications cutanées, Paris, Gaston Doin & Cie, 1942.

13. Birkhaug, K.: Protective Value of Intracutaneous and Percutaneous Methods of BCG Vaccination (Comparative Experimental Investigation), Acta med. Scandinav. **117**:274, 1944; BCG Vaccination in Scandinavia: Twenty Years of Uninterrupted Vaccination Against Tuberculosis, Am. Rev. Tuberc. **55**:234, 1947.

14. Gines, A. R., and Rebull Richieri, V.: Posición de la vacuna B.C.G. en la profilaxis de la tuberculosis, Rev. de tuberc. d. Uruguay **13**:255, 1945.

BCG VACCINATION IN CHICAGO

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CHICAGO

THE MEDICAL profession of the United States has been the most conservative in the world in accepting new vaccines, new drugs, or, in fact, any advance which has not been proved in this country, and particularly by members of the profession themselves. I recall quite vividly, when I was still young in the practice of pediatrics, that two of the leading pediatricians of that time were most reluctant to accept diphtheria toxoid. Smallpox vaccination was not universally accepted until the turn of the century, although it had had more than one hundred years of trial at that time. I am, therefore, not surprised that BCG is having its difficulties in being accepted in the United States.

REVIEW OF EXPERIMENTS

The first experiment in this country was begun in New York city by Park, Kereszturi and Mishulow in 1926.[1] They reported that by vaccinating children in tuberculous families, they were able to reduce the death rate from 2.8 to 0.5 per cent, although this work has been recently criticized by Levine because of the choice of controls. A review of the paper of Levine and his associates[2] reveals that they did not isolate children before and after vaccination. However, when they did so, the results were similar to those of Park, Kereszturi and Mishulow. Two other experiments in the United States were carried

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A paper presented before the Loyola University Chicago Pediatric Society, Oct. 14, 1947.

1. Park, W. H.; Kereszturi, C., and Mishulow, L.: Effect of Vaccination with BCG on Children from Tuberculous Families, J. A. M. A. **101**:1619 (Nov. 18) 1933.

2. Levine, M. I.; Vogel, P., and Rosenberg, H. A.: Immunization Against Tuberculosis: A Study of Essential Factors, Am. Rev. Tuberc. **38**:632, 1938. Levine, M. I.: An Evaluation of the Use of BCG in the Prevention of Tuberculosis in Infants and Children, Am. J. Pub. Health **37**:1089, 1947.

out by Aronson and Dannenberg, of Philadelphia,[3] and by Overton[4] of Nashville, Tenn. Both these studies revealed a definite protection from tuberculosis as a result of vaccination.

The report on the North American Indians,[5] studies on whom began after the institution of the one I am about to report on, was most encouraging. The study was conducted in four widely scattered reservations in the United States and in twelve communities in southeastern Alaska. During a six year period, 60 deaths from all causes occurred among 1,457 persons in the control group, compared with 34 among the 1,550 vaccinated. It may be stated that persons from 1 to 20 years of age were included in the study, and that there was no separation before or after vaccination. Twenty-eight deaths were assigned to tuberculosis among the controls, as compared with only 4 deaths among the group given BCG. The total incidence of all types of illness and deaths due to tuberculosis was 185 among the controls and 40 in the vaccinated.

I should like to say a word about the Scandinavian results in children. The writings of Wallgren, of Sweden,[6] are familiar to all. Up to the end of 1937 the number of children vaccinated with BCG was 1,069. He and his associates reported, after nine years, that 15 of the vaccinated children had died of nontuberculosis diseases. Only 2 cases of benign tuberculosis occurred, both of which healed completely. All vaccinated persons were observed to be in good health. Thus, 100 per cent of those persons examined were seen to be free of progressive tuberculous disease. Numerous reports from Sweden, Denmark and Norway have all indicated a definite lowering of the incidence of tuberculosis in the vaccinated children. Unfortunately, in the work done with children, although there was no question about the fact that a lowering of the tuberculosis rate was accomplished, the matter of having strict controls, as we in the United States expect, was not put into effect.

BCG VACCINATION IN CHICAGO

In 1933, when Dr. Tice, then president of the board of the City of Chicago Municipal Tuberculosis Sanitarium, conceived the idea of

3. Aronson, J. D., and Dannenberg, A. M.: Effect of Vaccination with BCG on Tuberculosis in Infancy and in Childhood: Correlation of Reactions to Tuberculin Tests, Roentgenologic Diagnosis and Mortality, Am. J. Dis. Child. **50**:1117 (Nov.) 1935.

4. Overton, J.: Observations on Use of BCG Vaccine in Nashville, Tennessee, South. M. J. **24**:878, 1931.

5. Aronson, J. D., and Palmer, C. E.: Experience with BCG Vaccine in the Control of Tuberculosis Among North American Indians, Pub. Health Rep. **61**:802, 1946.

6. Wallgren, A., cited by Birkhaug, K.: BCG Vaccination in Scandinavia: Twenty Years of Uninterrupted Vaccination Against Tuberculosis, Am. Rev. Tuberc. **55**:234, 1947.

having BCG introduced into Chicago, he offered Dr. Sol Roy Rosenthal, then studying in Europe, a fellowship in order to study the problem of BCG at the Institute Pasteur in Paris. Dr. Rosenthal accepted the fellowship and, after completing his studies there, brought back cultures to and set up a laboratory at the University of Illinois for a reevaluation of the safety of the vaccine on an experimental basis. After three years of such study, using thousands of animals, he definitely established that the bacillus of Calmette and Guérin failed to produce progressive tuberculosis. Then the question of vaccinating human subjects was considered. Quite a furor was aroused when this was proposed by Dr. Tice, so that Mayor Edward J. Kelly in 1936 appointed a committee to evaluate the problem. This committee was composed of Dr. Ernest E. Irons, professor of medicine and head of the department at the Rush Medical College; Dr. A. I. Kendall, then professor and head of the department of bacteriology at Northwestern University, now replaced by Dr. A. A. Day, who occupies the same position; Dr. Walter H. Theobald, professor of otolaryngology at the University of Illinois (and chairman of the board); Dr. Michael McGuire, professor of surgery at Loyola University, and myself. In March 1936, we met with Dr. L. Nègre, of the Institute Pasteur in Paris, who is a world authority on BCG. We inspected the BCG laboratories set up at the Cook County Hospital and known as the Tice Laboratories. Dr. Nègre heartily approved of the laboratories and gave them a certificate to that effect. Later, in that same month, Dr. Rosenthal presented to the Mayor's Committee the plan of procedure to be followed in the vaccination of human beings. The substance of this plan was that:

1. The vaccine would be assayed continuously in animals in order to make sure of its safety.

2. A control group, which in every way simulated the vaccinated group, was to be studied, the plan in this way differing from most of the experiments up to that time.

The study was to be made at the Cook County Hospital beginning in the prenatal clinic. Only those cases would be accepted for study in which the roentgenograms of the chest of every member of the household were negative for tuberculosis. This plan was approved by our committee. On March 2, 1937, the first child was vaccinated with BCG in Chicago. From that time on, the committee has met more or less on a yearly basis to review the results for the past year, and to make recommendations for the following year. The committee has now been functioning for eleven years. Recently, this same committee was reappointed by Mayor Martin H. Kennelly.

Up to the present the committee has approved the following plans of procedure:

1. Vaccination of newborn infants in nontuberculous households [7]
2. Vaccination of newborn infants in tuberculous households, with isolation in foster homes after vaccination [7]
3. Vaccination of nursing students [8]
4. Vaccination of medical students [8]
5. Vaccination of children of all age groups in two government housing projects and in two orphanages [9]
6. Vaccination of inmates of Manteno State Hospital [9]

RESULTS OF THE PROGRAM IN CHICAGO

The results on which I am going to dwell are those among infants and children. The first group of children, as already mentioned, was accepted for study in prenatal clinics. When the child was born, vaccination was performed after the third day of life. The infant was returned to the clinic after three months, after one year and then semiannually thereafter. Between visits to the clinic, field nurses visited the home. At the clinic visits the child was examined physically, given patch tests and examined roentgenographically. At the home visits the status of the child, the presence of other contacts and the social status were ascertained.

It was observed that 99.7 per cent of those vaccinated reacted to tuberculin after a single vaccination. Of these 79.85 per cent still reacted after six to six and one-half years. There were 11 children (among the 1,417 that were vaccinated) in whom roentgenograms of the chest showed evidence of a tuberculous infection, such as enlargement of hilar glands, infiltration of the lung and calcification. However, none of these lesions were seen twelve months after the onset except for calcification, showing that healing took place easily or that the infection was mild. On the other hand, there were 39 such children among the 1,414 controls. In a little less than half of them, the duration of the disease was more than twelve months, and in many of them it extended for two to three years. Three are still actively ill. But 1 death from tuberculosis occurred in the vaccinated group and 7 in the control group. The 1 death in the vaccinated group was that of a child in whom the vaccination was considered either a poor one or a "no take," as the reaction of the first Vollmer patch test was negative six and fifteen months after vaccination. The second patch test, performed

7. Rosenthal, S. R.; Blahd, M., and Leslie, E. I.: Ten Years' Experience with BCG (Experimental and Clinical), J. Pediat. **26**:470, 1945.

8. Rosenthal, S. R.: Use of BCG Vaccination Among Medical and Nursing Students, Hospitals **17**:75, 1943.

9. Rosenthal, S. R.; Leslie, E. I., and Loewinsohn, E.: BCG Vaccination in All Age Groups: Methods and Results of a Strictly Controlled Study, J. A. M. A. **136**:73 (Jan. 10) 1948.

immediately after the first, gave a weakly positive reaction. A Mantoux test was not done because of the poor cooperation of the parents.

In the group in which tuberculosis was present in the family and isolation was practiced in the vaccinated and the control series alike, 2 children among the 151 vaccinated on roentgenogram revealed changes that were considered tuberculous in nature. Again, recovery was noted after twelve months. Among the 105 controls, there were 5 with tuberculosis with 4 who died from the disease.

In the Ida B. Wells Housing Project, begun about five years ago, where negative reactors up to 10 years of age were alternately vaccinated and kept as controls, no cases of tuberculosis were seen in the 699 children vaccinated; whereas in the 625 control negative reactors, 4 showed roentgenographic evidence of tuberculosis, and among the 275 controls who reacted to tuberculin 2 others showed signs of the disease. Two deaths resulted from tuberculosis among the controls, 1 in a child whose tuberculin reaction was not recorded, but whose original roentgenogram was normal, and 1 in an originally positive reactor.

From these results it can be said that: (1) BCG vaccination is absolutely safe and (2) BCG vaccination prevents, up to a certain extent, the development of primary, virulent tuberculosis, as well as the primary, progressive phase of the disease.

THE FUTURE STATUS OF BCG VACCINATION

The questions that now arise are: How should BCG vaccination be used in the future? Who should receive the vaccination, and who should administer it? How well controlled should these studies be?

It is the feeling of the Mayor's Committee that BCG should not be distributed to the people at large; that only those who are highly susceptible to the disease and those who have excessive exposure should be the first to benefit from this form of vaccination. In order to obtain this objective, it is necessary that the work be carried out by organized health groups and not by the individual physicians. Such groups may be city health officials, tuberculosis control officers, tuberculosis control agencies, large hospital clinics or nurseries and state or national public health organizations.

To facilitate such a program along the most efficient and economical lines, it is proposed that city, county and state authorities join forces in a cooperative undertaking. Personnel should be trained in teams. Such a team should consist of 2 physicians, 2 clerks and 3 nurses, one of whom would act as supervisor. Vaccination should be carried on

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through the grammar school and the high school along the following general scheme:

After the necessary preliminary steps with existing tuberculosis control authorities, the local health commissioner, the superintendent of schools, the principals of the schools and, finally, the teachers have been taken, cards are to be distributed by the teachers of each classroom to be taken home by the child and signed by the parents.

On a definite schedule, the teacher should bring her pupils to a designated room in the school where tuberculin testing is to be done. Two strengths—1 : 5000 and 1 : 100 old tuberculin—are to be used in succession. Negative reactors are to be vaccinated, the matter of controls to be determined in each project. The cards are to be checked against the lists of active cases of tuberculosis in that community. Children living in a tuberculous household should not be vaccinated unless they can be separated from the source case for six weeks before and after vaccination. Positive reactors may be sent for roentgenographic examination of the chest if feasible. Follow-up study may be instituted at yearly intervals with tuberculin testing and chest roentgenogram if funds are available, otherwise it may be dispensed with. The efficacy can be determined by checking with letter or death reports.

Vaccination of newborn infants is the most economical and efficient approach. The following scheme is suggested:

1. There should be a joint program of health department and infant welfare organizations. A trained physician should make regularly scheduled visits to the maternity wards of such hospitals as are frequented by the group of people coming from highly infected districts.

2. Roentgenographic examination of the chest of the mother is to be insisted on. Vaccination is to be done after the third day of life or while the infant is in the hospital. The matter of controls should be determined by local authorities. A consent card must be signed by the mothers before vaccination.

3. Follow-up study can be easily effected through the infant welfare societies by their visiting nurses and their clinics.

4. Tuberculin patch tests can be done in the field and readings carried out in the clinic, if funds are available. Otherwise, such children may be followed by infant welfare records and death reports.

After the program is once established, it would be necessary to contact only the first year grammar and high school students yearly. Vaccination of newborn infants, however, is to continue as already described. All the records should be kept by the health authorities who have undertaken the study.

An Institution for Tuberculosis Research has been proposed, toward which the state has contributed money for the acquirement of property

and for the construction of a suitable building. This institution is to be under the direction of a board composed of members from the University of Illinois College of Medicine and the City of Chicago Municipal Tuberculosis Sanitarium. The operating expenses will be obtained from local, city, state, federal and private sources. To this end, a corporation has been formed, known as the Research Foundation, which is headed by Mr. Park Livingston, president of the board of trustees of the University of Illinois, and Mrs. Henry Pope Jr. The board of directors of this foundation is to be made up of leading public-minded citizens of the United States, the governor of Illinois, the board of directors of the Institution, the director of public health for the state of Illinois and a member of the United States Public Health Service. A medical advisory board made up of prominent physicians from the entire country, to include the Mayor's Committee, will govern the scientific end of the institution. It is hoped that this organization shall furnish BCG for the entire country. At present, the Tice Laboratories have been designated as the central laboratories for BCG production for the United States Public Health Service. In this capacity, vaccine has been supplied to the United States Public Health Service for its use in inaugurating programs in Columbus, Ga., and in Wayne County, Mich. In the capacity of consultant, Dr. Rosenthal assisted in these undertakings.

SUMMARY

1. The continuous thirteen year study of BCG in Chicago is the longest one of its kind in the United States.

2. In thousands of animals, as well as in human subjects, BCG was demonstrated to be absolutely safe.

3. In a group of newborn infants originating from a highly infected environment, but with no tuberculosis present in the immediate household, during a ten year period 1,417 were vaccinated and 1,414 kept as controls. In the vaccinated group roentgenograms of the chest of 11 children presented lesions which were considered to be on a tuberculous basis, as against 39 such instances in the control group. One death resulted from tuberculosis in the vaccinated, as against 7 in the control, group.

4. In a second series of children, in which there was tuberculosis in the immediate family and in which both vaccinated and control children were isolated in foster homes, 2 cases of tuberculosis, with no deaths, occurred among the 151 vaccinated, and 5 cases of tuberculosis and 4 deaths among the 105 controls.

5. In 699 vaccinated children up to 10 years of age, no cases of tuberculosis were seen over a five year period. In 625 controls who had a negative reaction to tuberculin, under similar conditions, there were 4 cases of tuberculosis. Among 275 controls, with positive reac-

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tions to tuberculin, 2 additional cases of tuberculosis and 1 death were recorded. Another death from tuberculosis occurred among the controls in whom the status of the tuberculin reaction was not known.

6. It is recommended, for the present, that BCG vaccination be carried on only in that portion of the population most susceptible to tuberculosis and in which the incidence of infection is unduly high.

7. The most economical and efficient manner of approaching this problem is through the grammar and the high schools, as well as the nurseries.

Hotel Del Prado (10).

COMPLICATIONS OF ASCARIASIS REQUIRING SURGICAL TREATMENT

Report of Case with Abdominothoracic Complications

ALTON OCHSNER, M.D.
ERNEST G. DeBAKEY, M.D.
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NEW ORLEANS

ALTHOUGH it is universally agreed that ascariasis is the commonest helminthic infection in man, comprehensive studies on tropical diseases rarely emphasize the fact that ascariasis can attain dangerous proportions necessitating immediate surgical intervention. This has led the medical profession to assume an attitude of benign tolerance toward the disease.

Complications of ascariasis requiring surgical intervention have been frequently recorded in the literature. Since they are usually of a serious nature and offer a rather poor prognosis, it is imperative that the diagnosis be made early and treatment be promptly instituted.

Human infection from Ascaris lumbricoides is commonly observed where unsanitary conditions and squalid personal hygiene prevail. Infection begins by swallowing the fully embryonated eggs, which pass down the intestine to develop into larvae. The larvae penetrate the walls of the small intestine, reach the lymphatics and venules and are carried through the right side of the heart to the lungs. After several days, they break through the pulmonary capillaries into the air sacs and are carried to the bronchioles, bronchi and trachea. They are then swallowed and pass to the small intestine where they develop into adult worms (fig. 1). In the event of massive inoculation, the larvae may pass through the left side of the heart and be filtered into the various organs of the body.

The types of lesion produced by Ascaris include mechanical obstruction produced by the adult worm and bacterial contamination transmitted by the migratory habits, migrating larvae and toxins.

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SURGICAL COMPLICATIONS

Since ascariasis is commoner in children, a higher incidence of surgical complications would be expected in them. On the other hand, these surgical complications are not infrequently encountered in adults, even elderly patients. Ascarides may produce mechanical obstruction in any hollow organ in the body, such as the trachea, intestine, bile or pancreatic ducts and others. Obstruction of the larynx resulting in suffocation has been reported.[1] Intestinal obstruction,[2] intussusception[3]

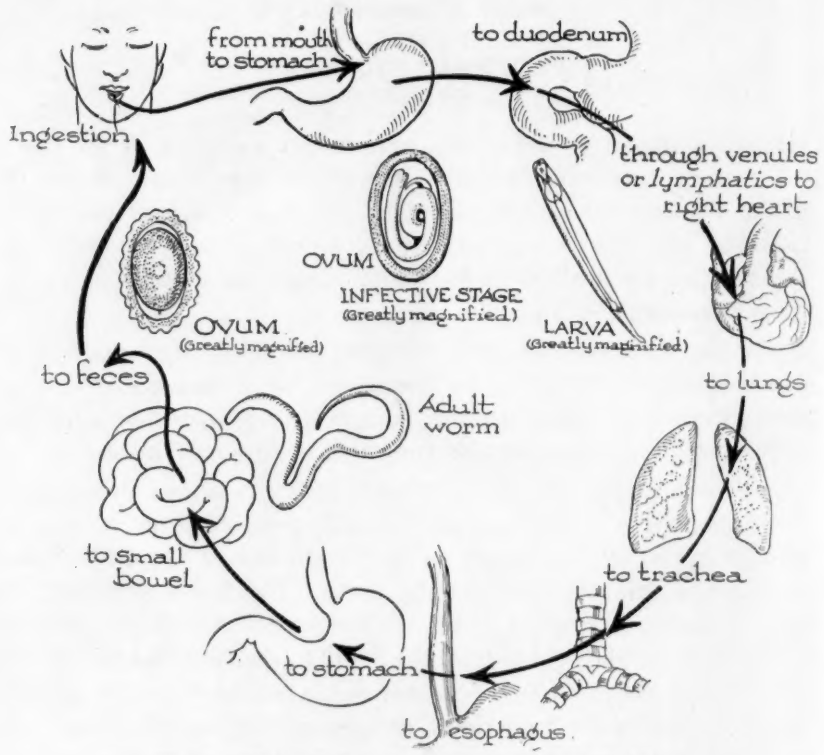

Fig. 1.—Diagrammatic life cycle of A. lumbricoides.

1. Millán, J. M., and Néspolo, J. F. V.: Obstrucción traqueal por áscaris, Prensa méd. argent. **25**:1070, 1938. Gentilucci, G.: Ileus and Accident from Ascaris Lumbricoides During Anesthesia, Policlinico (sez. prat.) **31**:839, 1924. Dixey, M. B. D.: Case of Sudden Death Due to Occlusion of Larynx by Two Ascaris Lumbricoides, Edinburgh M. J. **36**:111, 1929. Caldwell, F. C.: Death Caused by Ascarides, Am. J. Trop. Med. **2**:213, 1922.

2. (*a*) Watkins, T. H., and Moss, O. W.: Report of Two Cases of Intestinal Obstruction Caused by Roundworms Following Dosage of Santonin, J. A. M. A. **82**:1442 (May 3) 1924. (*b*) Whelan, C.: Intestinal Obstruction Due to Ascaris Lumbricoides, with Autopsy, ibid. **55**:1442 (Oct. 22) 1910. (*c*) Storck, A.; Rothschild, J. E., and Ochsner, A.: Intestinal Obstruction Due to Intraluminal Foreign

and volvulus [4] may result from ascariasis. Ascarides may accumulate and become entangled to form a bolus, resulting in partial or complete mechanical obstruction, which most commonly occurs in the terminal portion of the ileum because of narrowing of the lumen (fig. 2). An adequate explanation for the formation of a bolus has not been definitely established. Intussusception and volvulus may result from the presence of one or more worms, which needs not necessarily obliterate the intestinal lumen (fig. 3). It is thought that the irritating effect of these worms on the intestine stimulates hyperperistalsis and may be the initiating factor in the production of intussusception or volvulus.[5]

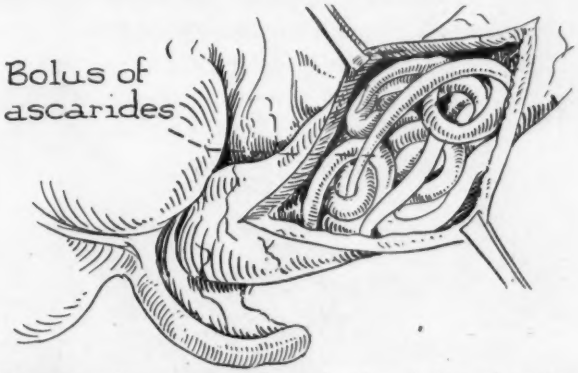

Fig. 2.—Diagrammatic representation showing bolus of worms producing complete obstruction.

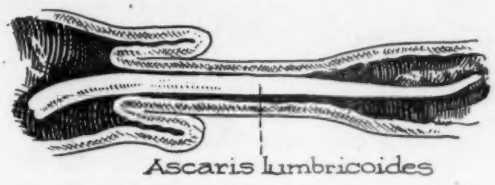

Fig. 3.—A. lumbricoides adhered to mucosa of small bowel producing intussusception.

Bodies, Ann. Surg. **109**:861, 1939. (*d*) Watson, F. C.: Intestinal Obstruction Due to Ascaris Lumbricoides, ibid. **71**:757, 1920. (*e*) Baugh, W. P.: Report of Case of Obstruction to Intestines Due to Ascaris, J. A. M. A. **80**:181 (Jan. 20) 1923. (*f*) Alles, F. C.: Acute Intestinal Obstruction Caused by Dense Accumulation of Roundworms, Brit. M. J. **2**:1001, 1924. (*g*) Levin, J. J., and Porter A.: Surgical and Parasitological Notes on Four Cases of Intestinal Obstruction Due to Accumulation of Very Large Numbers of Roundworms (Ascaris Lumbricoides), Brit. J. Surg. **11**:432, 1924.

3. McGlannon, A.: Intussusception in Acute Intestinal Obstruction, with Report of a Case Occurring with Roundworms, South. M. J. **9**:977, 1916.

4. Patoir, G., and Ledoux, J.: Volvulus d'une anse grêle obstruée par des Ascaris, Presse méd. **50**:643, 1942.

5. (*a*) Blanchard, R., cited by Girges, R.: Pathology and Complications of Ascariasis, J. Trop. Med. **37**:296, 1934. (*b*) McGlannon.[3]

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Storck, Rothschild and Ochsner [2c] reported 13 cases of intestinal obstruction due to ascarides of a total of 50 cases of intraluminal foreign bodies. Moss,[6] who reviewed the records at Charity Hospital, New Orleans, from 1929 to 1939, found 19 cases of intestinal obstruction due to ascarides, with a mortality rate of 68.3 per cent.

Perforation can occur in ulcerative lesions of the large and small intestine (fig. 4) with migration of the worms into the free peritoneal cavity.[5a] Freudenthal [7] reported a case of adult Ascaris in the free peritoneal cavity without evidence of any intestinal lesion. He stated that the most logical explanation is that the worm develops from the larval stage in the abdominal cavity. Blanchard [5a] was of the opinion

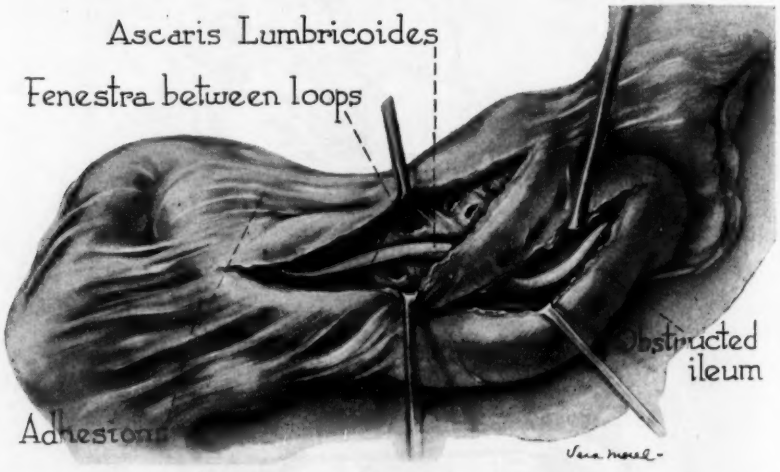

Fig. 4.—Illustration of a case encountered on the surgical service of Tulane University of Louisiana School of Medicine, showing intestinal ulcerations with perforation and invasion of an ascaris from one loop of intestine to another. (Courtesy of Dr. Ambrose Storck.)

that the process may be explained by nibbling of the mucosa, with resulting formation of abscess and subsequent pressure from the parasite producing the perforation. According to Milwidsky,[8] the attack on the intestinal wall, whether directly or by way of secretions from the worms, has not been settled. It is his opinion that the worms may settle in the mucous membrane and create sufficient damage to enable them to penetrate all layers. It is not uncommon to see ascarides in

6. Moss, E. H.: Personal communication to the authors.

7. Freudenthal, F.: Ascariasis of the Abdominal Cavity, Med. Klin. **19**:501, 1923.

8. Milwidsky, H.: The Surgical Complications of Ascariasis, Acta med. orient. **4**:370, 1945.

a suppurative and gangrenous appendix.[9] We recently performed an appendectomy on a young man for an acute inflammation of the appendix, with perforation of the tip by an adult ascaris (fig. 5). Whether the inflammatory process is due to the mechanical obstruction produced by these worms or to their irritating action is still controversial.[10] Of 1,000 surgically removed appendixes at Charity Hospital, New Orleans, examination of the fecal contents revealed ova of A. lumbricoides in 46 cases.[6] Einhorn and his associates [9f] reported a case of ruptured appendix in a child in which an adult ascaris protruded through a perforation in the tip of the appendix. Generalized peritonitis was present with several localized abscesses, the centers of which contained an adult ascaris. If the adult worm enters the free peritoneal cavity through a perforation of the intestine, localized or generalized peritonitis may result. We recently removed an appendix which was acutely inflamed and contained an adult ascaris (fig. 6). The adult Ascaris may find its way to any organ, with resultant formation of abscess.

Fig. 5.—Gangrenous appendix with perforation near the tip by an ascaris.

Maxwell [11] reported a case of tubo-ovarian abscess with an adult ascaris in its center. Sterling and Guay [12] found five adult live ascarides in the fallopian tube and a worm in the cul-de-sac surrounded by pus.

9. (*a*) Craig, C. F., and Faust, E. C.: Clinical Parasitology, ed. 3, Philadelphia, Lea & Febiger, 1943. (*b*) Flamini, S.: Perforation of Appendix by Ascarides in a Case of Acute Appendicitis, Riforma med. **54**:1701, 1938. (*c*) Lapeyre, J. L.: Adult Ascaris in Appendix, Presse méd. **44**:1787, 1936. (*d*) Frazer, W. P.: Appendicitis and Children: Report of Case with Intestinal Parasite, Virginia M. Monthly **64**:31, 1937. (*e*) Hester, W. S.: Surgical Complications of Ascariasis, South. Med. & Surg. **94**:572, 1932. (*f*) Einhorn, N. H.; Miller, J. F., and Whittier, L.: Ascariasis: Clinical Survey of One Hundred and Twenty-Five Cases of Infection with Ascaris Lumbricoides in Children, Am. J. Dis. Child. **69**:237 (April) 1945. (*g*) Cox, D. D.: Ascaris Lumbricoides as Cause of Appendicitis, J. Missouri M. A. **25**:527, 1928.

10. Vélez Rojas, H.: Pathologic and Clinical Study of Six Hundred and Thirty-Four Appendectomies, Bol. clin., Univ. Antioquia **9**:117, 1947.

11. Maxwell, J. P.: Tubo-Ovarian Abscess Containing a Live Ascaris Lumbricoides, J. Obst. & Gynaec. Brit. Emp. **31**:70, 1924.

12. Sterling, R., and Guay, A. J. L.: Invasion of the Female Generative Tract by Ascaris Lumbricoides, J. A. M. A. **107**:2046 (Dec. 19) 1936.

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The ascarides may enter the biliary or pancreatic radicles, producing obstruction and infection. This complication is not infrequent, as attested by the reports in the literature.[13] Although the mode of invasion of these organs is not definite, it is thought the worms find their way through the papilla of Vater (fig. 10). The absence of a duodenal papilla in the case we are reporting may have been a potential factor which predisposed to the invasion of ascarides into the common bile duct. Stiles [14] reported a female ascaris threaded through the eye of a large shoe button in the intestine and mentioned several similar cases. It was his opinion that these worms have a tendency to penetrate any

Fig. 6.—Photograph of inflamed appendix in which one adult ascaris was found.

13. (*a*) Brayne, W. F.: Ascaris in Bile Ducts, Brit. M. J. **2**:1122, 1925. (*b*) Rigby, H. M.: Acute Haemorrhagic Pancreatitis: Round Worm in Pancreatic Duct, Brit. J. Surg. **10**:419, 1923. (*c*) Gallie, W. E., and Brown, A.: Acute Hemorrhagic Pancreatitis Resulting from Roundworms, Am. J. Dis. Child. **27**:192 (Feb.) 1924. (*d*) Novis, I. M. S.: Partial Obstruction of the Pancreatic Duct by Round Worms, Brit. J. Surg. **10**:421, 1923. (*e*) Tyau, E. S.: Pathogenicity of Ascaris Lumbricoides, with Report of a Case, Nat. M. J. China **6**:21, 1920. (*f*) Morton, C. B.: Ascariasis of the Gallbladder: Literature and Case Report, Arch. Surg. **17**:324 (Aug.) 1928. (*g*) Estrada, J., and Garcia, E.: Ascaris Lumbricoides in the Common Bile Duct: Report of Case, J. Trop. Med. **45**:35, 1942. (*h*) Muir, J. B. G.: Removal of an Ascaris from the Common Bile Duct, Brit. M. J. **1**:1077, 1932. (*i*) Butt, A. P.: Roundworms in Gallbladder, Surg., Gynec. & Obst. **35**:215, 1922.

14. Stiles, C. W.: Ascaris Lumbricoides Caught in the Eye of a Shoe-Button, J. A. M. A. **76**:239 (Jan. 22) 1921.

opening. Prior to 1860, 37 cases of roundworms in the biliary system had been recorded in the literature.[15] In 1937, Aiga collected 76 cases of invasion of the biliary duct by ascarides and added 14 of his own.[16] Power and Johnston reported a case of ruptured empyema of the gallbladder associated with ascarides.[17] Gallagher[18] reported the case of a 52 year old woman with clinical evidence of obstruction of the common bile duct which proved to be due to an ascaris 8¼ inches (21 cm.) long coiled up in the duct. Acute hemorrhagic and suppurative pancreatitis has been discovered to be due to a worm blocking the ampulla of Vater or the duct of Wirsung.[19] Ch'in[20] reported a case of acute hemorrhagic pancreatitis due to impaction of an ascaris in the ampulla of Vater.

The migratory habits of these worms have led to grave complications.[21] Adams[22] reported a case of a 73 year old man with pain in the upper part of the abdomen in whom exploration revealed 3 liters of bile in the peritoneal cavity. Autopsy disclosed a rent in the hepatic duct through which an adult female ascaris protruded, resulting in the escape of bile. The gallbladder contained seven adult worms, and the bile ducts of the right lobe of the liver contained ten ascarides.

Hepatic abscesses due to ascariasis are usually multiple, and the pus is foul.[23] These abscesses may rupture into the peritoneal cavity[24] and occasionally into the thorax.[25] Crowell's[23a] case 1007 is somewhat similar to the case that we are reporting, in that a large abscess was observed on the dome of the right lobe of the liver, with thoracic

15. Frerichs, F. T.: A Clinical Treatise on Diseases of the Liver, translated by C. Murchison, New York, William Wood & Company, 1879, vol. 3, p. 181.

16. Aiga, Y.: Ueber Ascariden in den Gallenwegen, Arch. f. klin. Chir. **188**:600, 1937.

17. Power, R. W., and Johnston, H. W.: Case of Ruptured Empyema of Gall-Bladder Associated with Ascaris Lumbricoides, Brit. M. J. **1**:1086, 1930.

18. Gallagher, W. J.: Ascaris Lumbricoides Causing Common Duct Obstruction, J. Missouri M. A. **27**:170, 1930.

19. Rigby.[13b] Novis.[13d]

20. Ch'in, K. Y.: Acute Hemorrhagic Pancreatitis Due Probably to Impaction of Ascaris Lumbricoides in the Ampulla of Vater, China M. J. **47**:1373, 1933.

21. Altmann, F.: Ascaris Angiocholitis and Pancreatitis Due to Ascarides: Case, Wien. med. Wchnschr. **79**:428, 1929.

22. Adams, A. R. D.: Ascariasis of the Liver, Tr. Roy. Soc. Trop. Med. & Hyg. **28**:419, 1935.

23. (*a*) Crowell, B. C.: The Dangers of Ascariasis, Am. J. M. Sc. **159**:380, 1920. (*b*) Sivasambandan, R.: Multiple Abscesses in Liver Secondary to Ascaris Infection, Malayan M. J. **3**:101, 1928.

24. McNamara, K. N.: Ruptured Liver Abscess and Roundworms, New Zealand M. J. **42**:171, 1943.

25. Wyss, H.: Volvulus of the Ileum and Hepatic Abscess from Ascariasis Infection Seen at Operation: Two Cases, Schweiz. med. Wchnschr. **58**:502, 1928.

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empyema and gangrene of the lower lobe of the right lung. Wyss [25] reported a case of multiple hepatic abscesses with perforation into the pleural cavity.

The migrating larvae have been incriminated as the etiologic agent in certain cases of pneumonitis and bronchopneumonia.[26] Stewart [27] and Ransom [28] showed that in massive infection the larvae will produce bronchopneumonia. Koino [29] and his brother contracted severe pneumonia after swallowing many eggs in the infective stage. Larvae have been recovered from the sputum in some cases of pulmonary infection.[29] Wyss [25] described a case of pleural effusion in which ova were recovered. Empyema and pulmonary abscess may also occur.[30] Jenny [31] reported recovery of Ascaris eggs from the pleural exudate. As stated previously, in massive infection the larvae may pass through the left side of the heart and be filtered to the various tissues of the body with resultant inflammatory reactions. They have been seen in practically every organ of the body.[32]

There have been many toxic manifestations attributable to decomposition products of A. lumbricoides.[33] These products have been shown experimentally to contain anaphylaxin, hemolysins, neurotoxins and endocrinotoxins.[34] Urticaria, rhinitis and conjunctivitis may develop in laboratory workers who are sensitive to their emanations.[9a] Von Fellenberg [35] reported recurring attacks of urticaria in a mother each time her son had an Ascaris infection.

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26. Keller, A. E.; Casparis, H., and Leathers, W. S.: Clinical Study of Ascariasis, J. A. M. A. **97**:302 (Aug. 1) 1931.

27. Stewart, F. H.: Recent Experiments on the Life History of Ascaris Lumbricoides, Brit. M. J. **1**:102, 1919.

28. Ransom, B. H.: A Newly Recognized Cause of Pulmonary Disease—Ascaris Lumbricoides, J. A. M. A. **73**:1210 (Oct. 18) 1919.

29. Koino, S.: Experimental Infections on Human Body with Ascarides, Japan M. World **2**:317, 1922.

30. Middleton, L. A.: Pulmonary Gangrene with Empyaema and Acute Meningismus Due to Ascaris Lumbricoides, Canad. M. A. J. **20**:510, 1929.

31. Jenny, E.: Pleural Empyema Containing Ascaris Eggs in Patient with Ascariasis: Case, Schweiz. med. Wchnschr. **60**:266, 1930.

32. Carsten, M.: Ascaris Lumbricoides in Bladder, Deutsche med. Wchnschr. **53**:411, 1927. Boettiger, C., and Werne, J.: Ascaris Lumbricoides Found in Cavity of Human Heart, J. A. M. A. **93**:32 (July 6) 1929. Murray, H. E.: Ascaris Lumbricoides in Fallopian Tube, J. Obst. & Gynaec. Brit. Emp. **33**:448, 1926.

33. Manson-Bahr, P. H.: Manson's Tropical Diseases: A Manual of the Diseases of Warm Climates, ed. 12, Baltimore, William Wood & Company, 1945, p. 757.

34. Girges, R.: Pathogenic Factors in Ascariasis, J. Trop. Med. & Hyg. **37**:209, 1934.

35. Von Fellenberg, R.: Urticaria in Mother Caused by Hypersensitivity to Ascarides of Child, Schweiz. med. Wchnschr. **62**:582, 1932.

DIAGNOSTIC FACTORS

The presence of Ascaris infection in the various organs produces no pathognomonic symptomatic pattern. The symptoms of this infection depend on the organ involved, and the degree of severity is usually directly proportional to the susceptibility of the individual person. Massive infection in some persons may produce no ill effects, whereas in others with minimal infection grave complications may develop.

Since the small intestine is the natural habitat of ascarides, the commonest symptoms will be referable to this organ. They may vary from vague epigastric distress, nausea or vomiting, to the severe, excruciating abdominal pain of perforation or obstruction. Symptoms produced by invasion of ascarides to extraintestinal foci will not differ from those caused by other etiologic agents. These persons not infrequently vomit or pass worms. There may be associated systemic manifestations, such as anemia, fever, malnutrition, anorexia, lassitude, insomnia, urticaria, headaches and even convulsions. Sang [36] isolated a watery extract of Ascaris, called ascarase, which can inhibit the action of trypsin by combining with it. This may be a factor in the malnutrition that not infrequently accompanies this infection.

The diagnosis of ascariasis is dependent on recovering the ova from the stools or the larvae or adult worms from the involved organ. It has been shown by careful analysis of the reported cases that the history of vomiting or passing worms is equally significant. This fact has been frequently disregarded in establishing the preoperative diagnosis. Hematologic examination usually will reveal anemia and eosinophilia.[37] However, most authors doubt the diagnostic value of the latter finding. The roentgenogram may be of assistance in confirming the diagnosis. The pulmonary pattern is one of widening in the hilar areas, with increase in the bronchovascular markings.[38] The roentgenogram in intestinal ascariasis may reveal circular opacities corresponding to the diameter of the worms. If a light barium sulfate meal is feasible, stringlike shadows may be seen, due to the ingestion of barium sulfate by the ascarides.[39] In intestinal ascariasis it may be possible to palpate

36. Sang, J. H.: The Antiproteolytic Enzyme of Ascaris Lumbricoides Var. Suis, Parasitology **30**:141, 1938.

37. Perlingiero, J. G., and György, P.: Chronic Eosinophilia: Report of a Case with Necrosis of Liver, Pulmonary Infiltrations, Anemia and Ascaris Infestation, Am. J. Dis. Child. **1**:34 (Jan.) 1947.

38. Keller, A. E.; Hillstrom, H. T., and Gass, R. S.: Lungs of Children with Ascaris: Roentgenologic Study, J. A. M. A. **99**:1249 (Oct. 8) 1932. Manson-Bahr.[33]

39. Archer, V. W., and Peterson, C. H.: Roentgen Diagnosis of Ascariasis, J. A. M. A. **95**:1819 (Dec. 13) 1930. Fritz, O.: Askariden des Magendarmtraktes in Röntgenbild, Fortschr. a. d. Geb. d. Röntgenstrahlen **29**:591, 1922. Manson-Bahr.[33]

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a doughy abdominal mass which will give one a clue to the diagnosis. As a rule, the diagnosis is rarely made before operation because there are no characteristic signs or symptoms. However, the association of the history of passing or vomiting worms with other clinical observations is highly suggestive evidence of Ascaris infection. A positive diagnosis can be made only by the recovery of ova, larvae or worms.

THERAPY

Although drug therapy is somewhat irrelevant in this discussion, a word of caution is appropriate. The injudicious administration of anthelmintics and purgatives may result in definite ill effects. These include drug toxicity,[40] the absorption of highly toxic by-products of ascarides [33] and the migration of the worm to extraintestinal foci.[41] Hexylresorcinol is preferable to other anthelmintics because it is highly effective against Ascaris and practically harmless to the host.[9a] On the other hand, the vigorous employment of any anthelmintic may result in sudden death of the worms with absorption of their highly toxic by-products.[41] The commonest error in drug therapy is the too vigorous employment of purgatives which may produce intestinal obstruction due to mass accumulation of the worms or encourage their migratory proclivities.[41]

INTESTINAL OBSTRUCTION DUE TO ASCARIDES

The small intestine is the natural habitat of A. lumbricoides, and it is logical to assume that complications will develop most frequently in this organ. It is not uncommon for these worms to accumulate and form an entangled bolus which may completely occlude the intestine (fig. 2). The most frequent site of this obstruction is the terminal portion of the ileum because the small intestine gradually diminishes in size from its commencement to its termination. Manual disengagement of the Ascaris bolus without enterotomy is ineffective because of the tight interlacement of the ascarides. By gentle manipulation one may be able to disengage the entangled mass, but, even so, there is no assurance that the worms will not become entangled again and produce recurrent partial or complete obstruction. Therefore, enterotomy with evacuation is the only safe method of relieving the obstruction.

We recently performed exploratory operations on 2 children in whom the small intestine was literally packed with ascarides from the ligament of Treitz to the ileocecal valve (fig. 7). Both patients were treated with anthelmintic compounds after the operation. One recovered

40. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutrics for Physicians and Medical Students, New York, The Macmillan Company, 1941.

41. Faust: Personal communications to the authors.

and 1 died. The latter child vomited ascarides several times, and worms were observed crawling through the nose on several occasions. The cause of death was pneumonia which was thought to be due to aspiration. In such cases, enterotomy with evacuation of the worms is not practical because of the massive involvement. This maneuver would require milking or stripping the intestine for a considerable distance, a procedure which may traumatize the intestinal wall and thereby increase the chance of the parasites migrating to extraintestinal foci. Although we believe it is better to refrain from surgical intervention in such cases, the possibility of performing an ileostomy should be considered, a measure which will permit the uneventful migration of the ascarides through the artificial opening. It must be borne in mind that enterotomy is attended by some danger because remaining worms may penetrate the

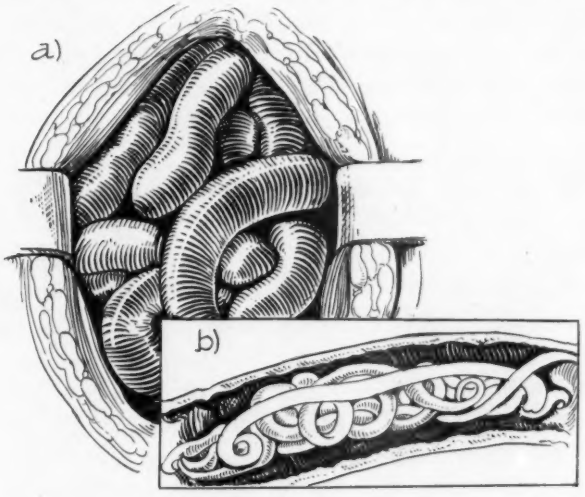

Fig. 7.—(*a*) Artist's conception of sausage-like small intestine packed with worms. (*b*) Sagittal section showing lumen filled with ascarides.

suture line.[42] For this reason, in known intestinal ascariasis, it is wise to institute specific drug therapy prior to elective operations.

In contrast to obstruction from an Ascaris bolus, intussusception and volvulus are usually associated with one or several worms which do not completely occlude the lumen (fig. 3). Therefore, surgical correction without enterotomy is the procedure of choice. Of course, if gangrene is present, resection is necessary.[43] Occasionally, one may find

42. (*a*) Kortzeborn, A.: Ascarides in Abdominal Cavity Causing Death After Resection of Stomach, München. med. Wchnschr. **71**:473, 1924. (*b*) Kneringer, V.: Passage of Ascaris Through Intestines and Abdominal Wall Following Gastric Resection for Cancer, Chirurg **13**:217, 1941. (*c*) Jaroschka, K.: Ascarid Ileus, Deutsche Ztschr. f. Chir. **178**:122, 1923.

43. Taylor, B. M.: Intestinal Obstruction from Ascarides, Am. J. Obst. & Gynec. **39**:800, 1899. Baugh.[2e]

perforations of the bowel with ascarides in the free peritoneal cavity. The treatment in such cases is essentially the same as that for any perforation. It is extremely important to inspect the intestine carefully for weakened areas and reenforce them so as to prevent subsequent perforations by remaining ascarides.[42c] Localized peritoneal abscesses may be encountered and, of course, demand drainage.

The diagnosis of obstruction of the common bile, cystic or pancreatic duct due to ascarides is usually made at the time of operation. Invasion of the gallbladder or cystic duct by these parasites requires cholecystectomy because of the concomitant infection. When ascarides are found in the gallbladder, they not infrequently are also present in the common duct. Therefore, in such cases regardless of the appearance of the choledochus, it should be diligently explored, for only in this way can one be assured that remaining ascarides will be recovered. T tube drainage should be instituted in all cases following exploration of the common duct. A soft rubber drain should be placed in Morison's pouch and brought out through the wound.

Obstruction of the common duct caused by one or more worms demands thorough exploration of the bile ducts and T tube drainage. In such cases frequently the gallbladder is diseased and, of course, should be removed. However, one may occasionally find a perfectly normal gallbladder, which should be left undisturbed.

An important decision to make regarding exploration of the common duct concerns drainage. If the duct has been invaded by ascarides, infection is present or likely to occur. In the presence of cholangitis, free drainage of the biliary tree is the treatment of choice. Decompression of the biliary radicles by drainage may encourage remaining worms to find their way into the duodenum. An ascaris has been known to make its exit through the T tube on the tenth postoperative day.[44] If for no other reason, T tube drainage is desirable from the standpoint of information obtained by injecting radiopaque oil through the tube and following its course under the fluoroscope. By this means it is possible to detect the presence of obstruction and even A. lumbricoides by the presence of circular opacities or sinuous lines.

Of extreme importance is the length of time T tube drainage should be employed. Drainage should be continued until the following criteria have been fulfilled in the order listed.

1. Infection has subsided and the temperature is near normal.

2. Adequate specific anthelmintic drugs have been administered and repeated examinations of the stool yield negative results.

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44. Yang, S. C. H., and Laube, P. J.: Biliary Ascariasis, Ann. Surg. **123**:299, 1946.

3. Evidence of patency of the biliary tree had been demonstrated by fluoroscopic examination during radiopaque instillation.[45]

4. The bile chloride determination approaches blood plasma chloride levels.[45]

5. Serum bilirubin determinations before and after the tube has been clamped for twenty-four hours have been compared. A word of caution might be appropriate in regard to clamping the tube for twenty-four hours. Whereas the experience of distress indicates obstruction to the normal flow of bile, the absence of pain or discomfort does not necessarily imply the normal egress of bile into the duodenum. The bile chloride and serum bilirubin determinations are important in that they indicate a return of normal hepatic function.[45]

Manifestation of involvement of the pancreas with ascarides may range from edema to hemorrhage, suppuration, necrosis or abscess. The decision concerning the desirability of operation for Ascaris infection of the pancreas cannot be based on accurate diagnosis. A careful and accurate appraisal of the status of the disease and the condition of the patient must be considered in the surgical management. If the clinical signs show continued improvement, operation should be deferred. On the other hand, surgical intervention should not be postponed if the patient fails to improve under adequate conservative management. Failure to improve may imply obstruction of the ampulla or duct of Wirsung by ascarides and requires further exploration. The procedure of choice will depend on the pathologic condition with which one is confronted. Edema of the pancreas may be controlled by decompression of the biliary tract. Diffuse hemorrhage, suppuration or abscesses will necessitate drainage. Novis [13d] reported a case of acute pancreatitis in a 12 year old Hindu girl in whom the pancreas was incised, the duct of Wirsung exposed and opened and two adult ascarides removed. Unless adequate drainage is established, pus may burrow up to the subdiaphragmatic spaces or down toward the pelvis or rupture into the general peritoneal cavity.

Hepatic abscesses produced by A. lumbricoides are usually multiple and offer a poor prognosis. Palpation may reveal a collection of worms which should be evacuated after the surrounding organs have been carefully walled off.[46] The abscess should be drained by a soft rubber drain, care being taken not to contaminate other serous cavities. Smear and culture determinations of the material will aid in further surgical management. Inaccessible lesions demand repeated, careful

45. Payne, R. L.: Postoperative Care in Surgery of the Bile Tract, J. A. M. A. **109**:1436 (Oct. 30) 1937.

46. Hartmann-Keppel, G. L.: Ascaridiasis of Billiary Apparatus, J. de chir. **21**:157, 1923.

and accurate examinations in order to determine the opportune period for extraperitoneal drainage. If there is considerable evidence of hepatic impairment and probable coexisting cholangitis, the biliary tract should be decompressed by means of T tube drainage.

Ascaris pneumonia has been suggested as a definite entity and may progress to empyema, pulmonary abscess or gangrene.[30] The surgical treatment of these conditions is similar to that in complications of pneumonia caused by other etiologic agents.

Use of general supportive therapy cannot be too strongly emphasized. Since these patients are usually anemic, debilitated and undernourished, they require multiple transfusions of whole blood. Specific

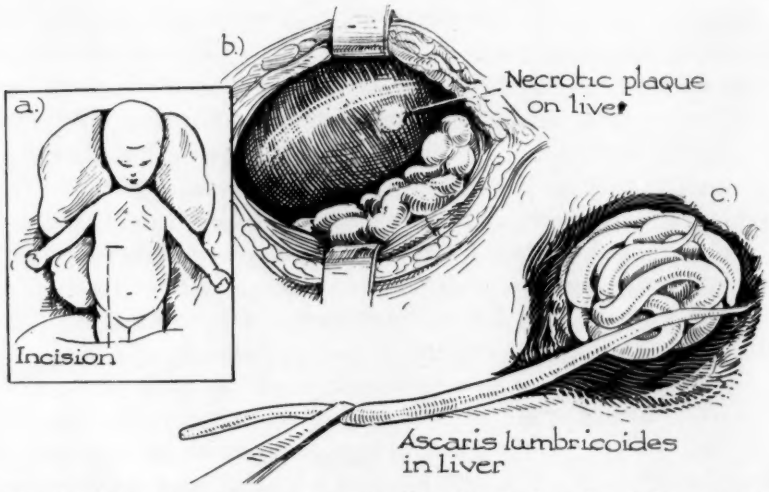

Fig. 8.—(*a*) Schematic drawings showing site of operative incision in infant with abdominothoracic complications of ascariasis; (*b*) abscess of liver due to ascariasis, and (*c*) appearance of opened abscess.

anthelmintic therapy should be judiciously administered until the host has been freed of the ascarides and repeated examinations of the stool have given negative results. Antibiotic substances should be given to control secondary infection. Intravenous administration of glucose is essential to patients with hepatic disease. Electrolyte balance should be maintained. A high caloric diet rich in vitamins should be given as soon as oral feedings are feasible.

REPORT OF CASE

A white baby girl, aged 20 months, a native of New Orleans, was admitted to the hospital on Nov. 2, 1946, because of anorexia, loss of weight and irritability of one month's duration. Five days before admission a cough developed, with expectoration and fever. The day prior to admission she vomited worms and passed worms in the stools.

The patient had been admitted to the hospital at the age of 5 months with measles and pneumonia and at 9 months for otitis media and diarrhea. Recovery was uneventful each time and examination of the stools on both admissions yielded negative results.

Physical examination on her admission revealed an acutely ill, undernourished, dehydrated and anemic infant weighing 19 pounds (8.6 Kg.). The temperature was 103 F., pulse rate 140 and respiratory rate 60 per minute. Rales were heard over both lower pulmonary fields. The abdomen was moderately distended, and there was considerable tenderness over the right upper quadrant. The liver was enlarged to 7 cm. below the costal margin.

The hematocrit reading was 32, and the white blood cell count 22,000, with no eosinophilia. Roentgenography revealed dilatation of the small intestine.

Obstruction of the small intestine produced by intussusception or by a bolus of Ascaris was suspected and exploration was recommended. Accordingly, on

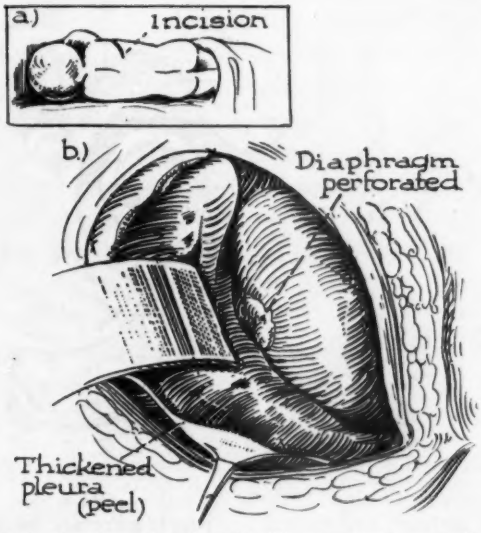

Fig. 9.—Schematic drawing showing details of second operation on infant with ascariasis; (*a*) posterolateral approach through sixth intercostal space, and (*b*) perforation of diaphragm and decortication of thickened pleura.

November 4, with the patient under anesthesia induced by the drop ether method the abdomen was opened through a right upper transverse incision. There was no obstruction in the gastrointestinal tract. The liver was greatly enlarged. A grayish white, necrotic exudate, 0.5 cm. in diameter, was noted on the anterior surface of the right lobe of the liver 3 cm. from the lower edge (fig. 8). When this was removed, an adult ascaris presented itself. Twenty-four adult worms were removed from this cavity, which measured 5 cm. in diameter and was lined with a necrotic exudate. Palpation revealed a similar mass high on the dome of the right lobe but due to its inaccessibility, evacuation was not attempted. Smear and cultures of the lesion in the liver yielded negative results.

After the operation, the baby received multiple small transfusions, glucose, penicillin and three courses of hexylresorcinol. Gradual improvement followed. Repeated examinations of the stool gave negative results. Roentgenograms of the subdiaphragmatic region were normal. The infant was closely observed for two

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months, during which time the temperature was normal, the appetite good and her general condition entirely satisfactory.

Approximately ten weeks after the operation, the patient contracted what was thought to be an infection of the upper respiratory tract with cough and fever. Examination revealed dulness over the right pulmonary base with evidence of fluid. A roentgenogram of the chest confirmed the physical findings. Thoracentesis on several occasions yielded from 10 to 50 cc. of clear amber fluid. The results of smear and cultures were reported as negative. Tenderness over the twelfth rib could not be elicited. Penicillin and general supportive therapy were continued, and the patient appeared to improve during the following two weeks, at the end of which time the temperature rose to 101.8 F. A roentgenogram at this time disclosed elevation of the diaphragm and fluid in the right pulmonary base. Repeated thoracenteses yielded from 15 to 75 cc. of cloudy, yellow fluid. Smears and cultures gave negative results. The patient failed to improve, despite the administration of antibiotic substances, multiple transfusions and general supportive therapy.

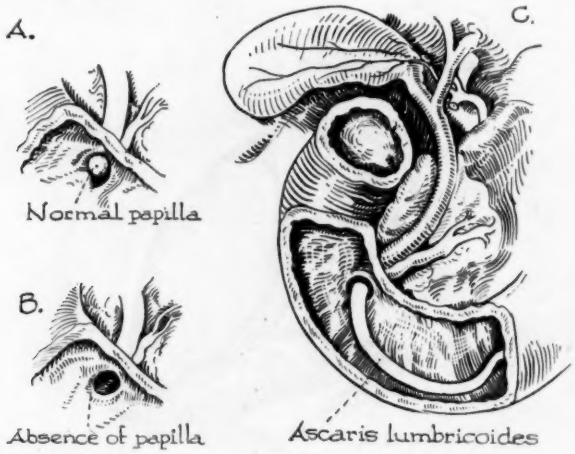

Fig. 10.—Drawings showing (*A*) the normal papilla which acts as a barrier to invasion of the ascarides; (*B*) absence of papilla increases the chance of invasion, and (*C*) probable mode of invasion of A. lumbricoides into pancreatic radicles.

Thoracotomy and possible decortication of the right lung were believed to be justified. Therefore, on Feb. 25, 1947, with the infant under cyclopropane anesthesia, a right thoracotomy was done. A small collection of cloudy, yellow fluid was present in the right hemithorax. There was considerable thickening of the entire visceral and parietal pleura. Over the dome of the right side of the diaphragm, a perforation 1.5 cm. in diameter communicated with a necrotic-lined cavity of the right lobe of the liver, 2 cm. in diameter (fig. 9). No ascarides were observed in the liver or thorax. The rent in the diaphragm was closed, and decortication of the right lung was accomplished. The thoracic cavity was closed without drainage. The patient was returned to the ward in fair condition. Results of culture and smears of the thoracic exudate were again reported negative. The postoperative course was stormy, and the patient died on the third postoperative day.

Autopsy revealed thickening of the parietal pleura of the right hemithorax, with several small pinpoint abscesses pocketed in the parietal pleura overlying

the right portion of the diaphragm. The suture line closing the opening in the diaphragm was intact. The cavity in the liver under this area measured 2 cm. but contained neither ascarides nor pus. The liver weighed 500 Gm. A subcutaneous abscess, measuring 2.5 cm. in diameter, posterior to the primary abdominal incision, was observed extending into the hepatic parenchyma for a distance of 7 mm. The previous cavity from which twenty-four worms had been evacuated was replaced by fibrous tissue. No worms were seen in the gastrointestinal tract. No true duodenal papilla was observed (fig. 10). The opening into the duodenum measured 4 mm. in diameter. Culture and smears from the hemithorax and liver yielded negative results.

The anatomic diagnoses were subcutaneous abscess, two hepatic abscesses and multiple pinpoint abscesses in the right parietal pleura, measuring 1 to 3 mm. in diameter, status after thoracotomy and decortication and agenesis of duodenal papilla (fig. 10).

COMMENT

In all probability, if the hepatic abscess on the dome of the right lobe of the liver had been timely drained, pleural perforation would have been averted. Definite signs and symptoms, such as tenderness over the twelfth rib, fever and elevation and immobility of the diaphragm, indicate the necessity for immediate subdiaphragmatic extraperitoneal drainage. The absence of these manifestations, together with general improvement and apparent recovery over a two month period, led us to assume that the abscess had spontaneously resolved. The intensive antibiotic therapy may have been a factor which inhibited progression of the pathologic process.

Failure to recognize the true pathologic condition when the infection of the upper respiratory tract and pleural effusion developed was a serious error. If subdiaphragmatic extraperitoneal drainage had been accomplished even at this time, pleural perforation might have been averted. Twenty-four hours after the onset of the infection of the upper respiratory tract, it was realized that this represented perforation of the hepatic abscess into the right pleural cavity. The repeated negative results of smears and cultures of the pleural fluid and general improvement justified further conservative management.

After two weeks of conservative therapy, it was apparent that drainage was inadequate and surgical intervention was necessary. Since mediastinal fixation had been established, thoracotomy and possible decortication were considered. At the time of thoracic exploration, it was believed that decortication could be done without difficulty and thereby obviate another operation. This procedure proved to be too shocking and most likely was responsible for the infant's death.

SUMMARY

1. Although ascariasis is the commonest helminthic infection in man and is usually a benign condition, if surgical complications develop, it becomes a more serious disease, with a high mortality rate.

2. Pathologic lesions in ascariasis are dependent on mechanical obstruction, bacterial contamination, migrating larvae and toxic reactions.

3. Since there are no pathognomonic signs or symptoms of this infection, one should be highly suspicious when a history of vomiting or passing worms is elicited.

4. Whereas intraluminal intestinal obstruction due to ascarides demands immediate exploration, with enterotomy and evacuation of the bolus, those masses not producing obstruction of the lumen should be left undisturbed.

5. Localized abscesses due to Ascaris lumbricoides may occur in any organ and demand adequate drainage. Hepatic abscesses are usually multiple and should be evacuated in a manner which will not contaminate other organs.

6. Invasion of the gallbladder by ascarides demands cholecystectomy, with exploration and drainage of the common bile duct. Obstruction of the common bile duct requires diligent exploration and T tube drainage.

7. In known intestinal infection with A. lumbricoides, elective operation on the gastrointestinal tract should be delayed until adequate specific drugs have been administered.

8. Anthelmintic drug therapy is not without danger and should be judiciously administered.

9. Patients with this infection are usually anemic, malnourished and debilitated and require multiple transfusions of whole blood, restoration of electrolyte balance and a high vitamin, high caloric diet.

10. A report of a case, with discussion of surgical complications, is presented.

NOTE.—Since this article was submitted for publication, a 2 year old sister of the patient reported on in this paper was admitted to the hospital, on April 19, 1948. She vomited ascarides on the evening of April 18 and the morning of April 19. Anorexia and loss of weight were noted for several weeks prior to admission. At the age of 12 months, a diagnosis of ascariasis was made and specific therapy administered.

On her admission, examination revealed an acutely ill and undernourished white girl. Temperature was 105.4 F., pulse rate 150 and respiratory rate 34. The weight was 21 pounds (9.5 Kg.). There were 3,600,000 red blood cells and 6,300 white blood cells, with 54 per cent polymorphonuclear leukocytes, 37 per cent lymphocytes, 6 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils. The blood

chloride measured 544 mg. per hundred cubic centimeters and the carbon dioxide–combining power, 20 volumes per cent.

Therapy consisted of blood, fluids, penicillin and, on April 23, 0.2 Gm. of a pill containing hexylresorcinal (crystoids anthelmintic®).

She died on the sixth day in the hospital. Autopsy revealed moderate enlargement of the liver. An abscess of the right lobe of the liver, 12 cm. in diameter, with no evidence of ascarides, was observed. It is believed that this represented an Ascaris infection which had undergone disintegration and necrosis. There were many adult worms in the small bowel.

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Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

SELF SELECTION OF DIET: III. APPETITES FOR B VITAMINS. E. M. SCOTT and ELEANOR QUINT, J. Nutrition **32**:285 (Sept.) 1946.

Scott and Quint by their experiments showed that appetites for foods containing thiamine, riboflavin or pyridoxine are developed in rats whose diets have been deficient, respectively, in these vitamins. Such appetites are not simple preferences, because they cannot be demonstrated in normal animals. It was also concluded that the appetite for foods containing pantothenic acid is a learned appetite and not a true hunger.

FREDEEN, Kansas City, Mo.

SELF SELECTION OF DIET: IV. APPETITE FOR PROTEIN. E. M. SCOTT and ELEANOR QUINT, J. Nutrition **32**:293 (Sept.) 1946.

Scott and Quint concluded that the appetite in rats for various proteins were largely independent and that no "appetite for protein" in the general sense was indicated.

FREDEEN, Kansas City, Mo.

THE UTILIZATION OF CALCIUM IN SOYBEAN PRODUCTS AND OTHER CALCIUM SOURCES. LAWRENCE J. SCHROEDER, WILLIAM M. CAHILL and ARTHUR H. SMITH, J. Nutrition **32**:413 (Oct.) 1946.

Schroeder and his associates studied the utilization of the calcium in three foods and one pure chemical compound in adult human subjects. The supplementary calcium consumed ranged from 319 to 795 mg. per day. The average per cent utilization of the calcium in evaporated milk was observed to be 29.1, in calcium sulfate, 23.7, in soybean "milk," 22.6 and in whole cooked soybeans, 10.4.

FREDEEN, Kansas City, Mo.

Vitamins; Avitaminoses

CANITIES AND ALOPECIA IN CHILDREN ASSOCIATED WITH AVITAMINOSIS: PRELIMINARY REPORT. ANTONIO PEÑA CHAVARRÍA, LEON GOLDMAN, C. SAÉNZ-HERRERA and E. CORDERO-CARVAJAL, J. A. M. A. **132**:570 (Nov. 9) 1946.

In Costa Rica, infants and young children with severe avitaminosis, especially vitamin A deficiency, pellagra, riboflavin deficiency, beriberi, nutritional edemas or mixed syndromes of avitaminosis, were observed to exhibit characteristic associated changes in the hair, both loss, diffuse or especially pronounced in the frontal area, and depigmentation. These changes are easily reversible if the patient survives the severe vitamin deficiency state. Improvement may be produced by a general, adequate diet if it is utilized alone or together with polyvitamin mixtures of the B complex. The addition of biotin is thought, but not proved, to accelerate over other therapies the return of normal growth and pigmentation to the hair. Similar changes were not observed in the hair of adults with decided vitamin deficiency syndromes.

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OCULAR CHANGES IN A CASE OF RIBOFLAVIN DEFICIENCY. G. BASSI and S. JONA, Boll. d'ocul. **24**:3, 1945.

A 12 year old boy presented the following ocular changes: (1) superficial corneal vascularization, (2) pericorneal injection, (3) clouded aqueous and (4) lacrimation and photophobia. After the daily administration of riboflavin, the ocular lesions disappeared completely, only to recur when treatment was discontinued.

G. BIETTI. [ARCH. OPHTH.]

VITAMIN D METABOLISM: III. EFFECTS OF INTRAMUSCULAR INJECTION OF VITAMIN D ON METABOLISM OF CALCIUM AND PHOSPHORUS IN INFANTS. RENÉ HOUET, Ann. pædiat. **167**:128 (Sept.) 1946.

Every suckling of a series, whether rachitic or not, when given 15 mg. of vitamin D parenterally showed a slight increase in urinary excretion of calcium and a great increase in that of phosphorus. Maximum values were attained a little later than with oral administration of the vitamin.

Rapid improvement in calcium and phosphorus absorption in the intestine was seen in rachitic children, while no increase in absorption was noted in the normal ones. The calcium balance remained unchanged in normal children but improved rapidly in the rachitic ones. In the normal children, the phosphorus balance decreased at first but returned to the values present before the administration of the vitamin. Phosphorus balance showed great improvement, however, in the rachitic children. When given in doses of 15 mg., there was no difference in the action of vitamins D_2 and D_3 whether administered orally or parenterally.

The author reviews the literature on vitamin D absorption.

FROM THE AUTHOR'S SUMMARY.

Newborn

THE RH FACTOR AND ERYTHROBLASTOSIS. C. E. SNELLING, Canad. M. A. J. **56**:47 (Jan.) 1947.

This is a review of the literature on erythroblastosis fetalis, with a discussion of the patients with the disease admitted to the Hospital for Sick Children, Toronto, Canada, since 1935.

One hundred and forty-three patients were admitted, with a mortality rate of 43.3 per cent. The outstanding symptoms were jaundice in 81 patients, with the condition dating from birth in 65 and with a later onset in 16. Pallor alone appeared in 16 patients, cyanosis alone in 5. Purpuric spots with jaundice or pallor were evident in 9, while 6 showed edema with jaundice. Hemorrhage occurred in 4 patients.

Fifty-nine patients were tested for antibodies in the mother's blood; 23 showed high antibody titers; 13, moderate titers, and 23, nothing significant, while 4 were of a rare blood group.

Breast milk in 11 mothers was tested for the presence of antibodies; 7 showed the antibodies, while in 4 they were not found.

MOORE, OMAHA.

NEONATAL IMMATURITY IN THE WAR PERIOD. L. CUSMANO, Lattante **18**:9 (Jan.) 1947.

Statistics are reported from the records of the obstetric clinic in Parma, Italy, the five war years (1942 to 1946) being compared with the five prewar years (1937 to 1941). Infants weighing under 2,500 Gm. at birth were classified as

immature. The frequency of the birth of immature infants in the prewar years was 509 of 5,689 births (8.8 per cent) and in the war years 494 of 4,031 births (12.3 per cent). The highest percentage was in 1944 (17.6 per cent). The increase was in the number of infants weighing between 2,000 and 2,500 Gm., and not in the number of infants under that weight. The ratio of the percentages of stillbirths was lower in the war years (16.2 to 17.7 per cent), but the ratio of the percentages of neonatal deaths was higher (16.6 to 15.7 per cent). Maternal illness or toxemia was responsible for 32.4 per cent of the immature infants in the prewar years as compared to 29.2 per cent in the war years.

HIGGINS, Boston.

STREPTOCOCCIC EMPYEMA IN A 15 DAY OLD INFANT TREATED WITH PENICILLIN GIVEN INTRAPLEURALLY. G. MAINI, Lattante **18**:91 (Feb.) 1947.

An infant girl, 15 days old, had empyema due to hemolytic streptococcus. The condition was probably contracted from the mother who had puerperal sepsis. Penicillin was given intrapleurally and intramuscularly four times on alternate days. The child recovered.

HIGGINS, Boston.

TREATMENT OF STAPHYLOCOCCIC SEPSIS IN A 15 DAY OLD INFANT. A. SIMONINI, Lattante **18**:98 (Feb.) 1947.

A 15 day old infant with staphylococcic septicemia and abscesses at the umbilicus, the elbow, the knee and the hip failed to respond to sulfonamide therapy or anatoxin. Penicillin therapy, however, cured the infection.

HIGGINS, Boston.

AN EPIDEMIC OF DIARRHEA OF THE NEWBORN IN MILAN: BACTERIOLOGIC STUDY OF THE PATHOGENIC AGENTS. NELLA ELETTI, Lattante **18**:199 (April) 1947.

An epidemic of diarrhea involving 60 newborn infants occurred in the Provincial Maternity Hospital, of Milan, Italy, in June and July 1946. Three infants died. Studies were made of the fecal flora in 7 infants. A strain of Escherichia coli (group B) and enterococci were isolated from each infant, and the toxicity of the organisms was tested in mice. Maximum toxicity was found with mixed cultures, and with the E. coli organisms and a broth filtrate of the enterococci. The enterococci alone did not kill the mice.

HIGGINS, Boston.

Acute Contagious Diseases

SEROLOGIC TYPES OF HEMOLYTIC STREPTOCOCCI IN SCARLET FEVER IN MASSACHUSETTS. G. E. FOLEY, W. L. AYCOCK AND R. D. COX, New England J. Med. **233**:761 (Dec. 20) 1945.

During the past year, a total of 839 throat swabs were examined, of which 640 (76.3 per cent) were positive for group A hemolytic streptococci. Hemolytic streptococci associated with scarlet fever in certain Massachusetts communities during 1944, in order of their frequency, were, predominantly, types 2, 1, 8 and 19. Similar distributions of types for 1942 and 1943 were obtained in the study previously reported. During the three year period of this study, there was some shifting of types in relative order of frequency, but type 2 seemed to maintain itself as a major cause of scarlet fever.

During the course of this study, 1,067 cases of scarlet fever were classified with respect to the serologic type of the streptococcus, nineteen types being encountered. The frequency with which a given type was isolated in cases of nonscarlatinal infection was essentially the same as that in cases of scarlet fever.

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Additional observations on multiple cases in the same family indicate that household outbreaks are usually due to a single serologic type. GENGENBACH, Denver.

THE PSYCHIC REACTION IN POLIOMYELITIS. ANGIOLA BORRINO, Pediatria **54**:529, 1946.

The author points out particular alterations of mood and behavior in children with acute anterior poliomyelitis (Heine-Medin disease): a singular lapse with weeping and sadness during the first phase of the illness, followed, during the phase of regression, with the return of the first movements, by the coming back to serenity and vivacity. She thinks the "psychic component" has a certain importance, not only for early diagnosis but especially in the development and the prognosis. She believes that early motor therapy should be aided by psychic stimulation (persuasion, suggestion, encouragement) to utilize the active residual energy and the subsidiary action of muscles with innervation still unaffected.

FROM THE AUTHOR'S SUMMARY.

EPIDEMIOLOGY OF ACUTE ANTERIOR POLIOMYELITIS. G. D. HEMMES, Nederl. tijdschr. v. geneesk. **91**:368 (Feb. 15) 1947.

Widely discussed facts concerning the spreading of poliomyelitis in Netherlands during the period from Sept 1, 1923 to Dec. 31, 1945 are mentioned. The occurrence of silent immunization *(stille Feiung)* in poliomyelitis is denied. The hypothesis is advanced that the virus excreted by human patients cannot infect others directly when passed along in the natural manner. The direction which prolonged investigations should take is indicated.

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

IMMUNIZATION WITH THE VOLE BACILLUS. KONRAD BIRKHAUG, Am. Rev. Tuberc. **53**:411 (May) 1946.

The interesting researches carried on at Oxford University on the value of a prophylactic vaccine made from vole acid-fast bacilli against human tuberculosis were interrupted by the war. Wild voles (Microtus agnestis) from various localities in the British Isles were observed to have an epizootic disease. The caseous lesions present in these animals contained masses of acid-fast bacilli which proved to represent a new type of tubercle bacillus. Preliminary studies of the immunizing power of material from these lesions were made, using animals infected with bovine and human tubercle bacilli. When these experiments were interrupted by the war, cultures of the vole acid-fast bacillus were smuggled into Norway, where the studies reported in this paper were carried out. The British workers, Wells and Brooke, from their preliminary observations made the statement: "Vaccination of guinea pigs with the vole acid-fast bacillus prior to infection with virulent mammalian tubercle bacilli gives a degree of protection which apparently is far greater than has been recorded by other means" (*Brit. J. Exper. Path.* **21**:104, 1940).

With the material sent him, Birkhaug was able to continue the animal experiments and to observe his animals for longer periods of time. He also made a comparative study of immunity conferred by the vole vaccine and BCG. With greater facilities for prolonged observation of infected animals, he concludes that intracutaneous vaccination of guinea pigs with the vole acid-fast bacillus (Wells), prior to infection with virulent human tubercle bacilli, gives a high degree of protection which is equal to, but not greater than, that produced by vaccination with BCG.

SMITH, Ogden, Utah.

RESULTS OF BCG IMMUNIZATION IN NEW YORK CITY. MILTON I. LEVINE and MARGARET F. SACKETT, Am. Rev. Tuberc. **53**:517 (June) 1946.

This report summarizes the results of studies on the value of BCG as an immunizing agent against tuberculosis during a ten year period. While more than 2,000,000 children have been vaccinated with BCG throughout the world, and most of the results of such vaccinations have been reported favorable, the vast majority of these studies have been inadequately controlled.

That the selection of controls is important became evident early in the present study. In a group of children observed before a carefully worked-out selection of controls was devised, mortality due to tuberculosis in the vaccinated group was 0.68 per cent as compared with 3.38 per cent in controls. The mortality in a group of about equal numbers in which controls were more carefully selected was 1.41 per cent in the vaccinated children and 1.51 per cent among the controls.

All the children, when first observed, with rare exceptions, were under 12 months of age and came from tuberculous families. During the first two years of the study the vaccine was given orally during the first ten days of life. By this method approximately 50 per cent developed positive reactions to tuberculin. Thereafter, the parenteral method of vaccination was used, which resulted in the development of approximately 85 per cent positive reactions to tuberculin tests.

The conclusion drawn from this carefully controlled and prolonged study was that routine separation of children for three months before and three months after BCG vaccination, to eliminate the hazard of contagious contamination with human tubercle bacilli, was not a feasible or safe procedure. A small sample in which such separation was possible indicated that the BCG vaccination might have protective value were such separation possible. From a public health standpoint, the value of BCG must be judged by its ability to reduce mortality due to tuberculosis in children vaccinated in their homes in a tuberculous environment. As a public health measure, the routine vaccination with BCG of children from tuberculous homes is less advantageous than removal of the tuberculous subject from the home.

SMITH, Ogden, Utah.

ADEQUATE DIET IN TUBERCULOSIS. FRANCIS M. POTTENGER JR. and FRANCIS M. POTTENGER, Am. Rev. Tuberc. **54**:213 (Sept.) 1946.

The experience of the Pottengers in their sanatorium over a period of many years has convinced them of the value of a high protein, high fat, low carbohydrate diet, rich in natural vitamins, in the treatment of active tuberculosis. Whole grains are used in cereals and breads in order to provide adequate minerals. Fertile eggs of hatching quality are served because of their superiority in estrogenic substances. Certified raw milk is used in place of heat-treated milk since the former contains important enzymes necessary to calcium metabolism. Visceral meats are used whenever possible. Meats and other foods are altered as little as possible by applying low temperatures in cooking. Raw liver served in tomato juice is an excellent source of minerals and vitamins. Animal fats, including butter, are better tolerated than vegetable fats. Extensive use is made of gelatin, which serves as a hydrophilous base to the contents of the stomach, reducing the irritation of the gastric mucosa. Analysis of this diet and sample menus are detailed in the article.

The use of this vital diet apparently increases the resistance of the tuberculous person to his disease and improves muscle tone, often in spite of lack of exercise. In a group of children maintained on this diet tuberculin reactions became negative

in many. The authors feel that the improved diet contributed in large measure to this loss of sensitivity to tuberculin. The same type of diet has been used in the treatment of a group of allergic children with good results.

SMITH, Ogden, Utah.

BCG VACCINATION IN HOSPITALS AND SANATORIA OF SASKATCHEWAN. R. G. FERGUSON, Am. Rev. Tuberc. **54**:325 (Oct.-Nov.) 1946.

The frequency with which tuberculosis developed in the nurses and other employees in hospitals and sanatoriums created a condition which threatened the efficient prosecution of the antituberculosis campaign in the province of Saskatchewan. After a five year observation period the findings were: About 80 per cent of each class of nurses entering training since 1934 had had a negative reaction to tuberculin. By far the highest incidence of tuberculosis occurred among exposed persons who had had negative reactions to tuberculin on entering service. Despite the institution of preventive measures, little or no improvement in protection of exposed persons appeared to have been accomplished.

BCG vaccination of tuberculin-negative personnel was commenced in 1938. No attempt at segregation was made during the process of vaccination. This report covers the period from 1938 to March 1945 and may be summarized as follows: BCG vaccination of nurses with negative reactions to tuberculin on entrance to a general hospital environment, where the rate of infection was 12 per cent per year among the nonvaccinated negative reactors, and the duration of exposure was 2.42 years, reduced the number of cases of manifest tuberculosis that developed to a ratio of 1 : 4.27, as compared with nonvaccinated negative reactors.

Among employees of sanatoriums, in whom the rate of infection among nonvaccinated negative reactors was 60 per cent during the first year of exposure, the number of cases of manifest tuberculosis that developed in vaccinated persons with negative reactions was reduced to a ratio of 1 : 5.03, as compared with nonvaccinated negative reactors. A further observation was that in the cases of manifest tuberculosis which did develop among the vaccinated employees, the lesions were less extensive. This study was carried out by the National Research Council of Canada.

SMITH, Ogden, Utah.

MANAGEMENT OF PRIMARY TUBERCULOSIS IN CHILDREN. R. V. PLATOU, Am. Rev. Tuberc. **55**:341 (April) 1947.

There is a surprising lack of unanimity of medical opinion regarding management of children who react positively to cutaneous tests with tuberculin. If such children do not appear ill, the prevalent attitude is usually one of complacency, which may be warranted for the majority of cases, but the experience of Platou at the Charity Hospital, in New Orleans, convinced him of the dangers inherent in this ordinarily benign phase of tuberculosis.

During the ten years from July 1936 to July 1946, 153 deaths occurred among 784 recognized clinical cases of tuberculosis in 82,000 children admitted to this hospital. Tuberculosis accounted for more than 6 per cent of all deaths in children. One hundred and fourteen of the 153 deaths occurred before the fifth year of life.

In studying the history of the fatal cases, the author observed that the first symptoms which could even retrospectively be attributed to tuberculosis were ordinarily mild and rarely led to medical examination until weeks or months had passed. Definite symptoms characterizing the terminal episode were usually present for about three weeks before medical examination and hospitalization. More than 80 per cent of the children died within three weeks of admission. From these

observations, it would seem that the earlier the infection occurs, the more pessimistic and careful must be predictions as to its ultimate course. There is no place for complacency when a positively reacting infant or child is encountered. The physician when confronted with such a child has six clearcut responsibilities:

He must classify or describe the lesion, judge its activity, determine communicability, seek sources of infection, make recommendations for therapy based on specific objective data and follow the patient carefully at frequent intervals, at least until all activity has subsided or until resolution of the initial lesion is complete.

SMITH, Ogden, Utah.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

REPORT OF A CASE OF RUPTURED STOMACH IN AN INFANT THREE DAYS OLD. EUGENE P. PENDERGRASS and ROBERT E. BOOTH, Am. J. Roentgenol. **56**:590 (Nov.) 1946.

Rupture of the stomach in young infants is a rare condition. The cases reported in the literature have been considered to be secondary to the presence of gastric ulcer.

This report gives the history, results of physical examination and operative and autopsy observations on a case of ruptured stomach in a 3 day old infant. A definite etiologic factor was not demonstrated.

HARRISON, Chicago.

CARDIOSPASM IN AN INFANT. FEDERICO GÓMEZ, Bol. méd. d. Hosp. inf., México **1**:11 (July-Aug.) 1944.

A 13 month old boy, weighing 5.65 Kg., was admitted to the hospital complaining of projectile vomiting since birth. The laboratory reported the absence of gastric juice in the vomitus; this datum, together with the roentgenogram and the clinical findings confirmed the diagnosis.

The basis for treatment was rest and administration of transfusions, small high caloric feedings, supplementary vitamins and fluids. With this, the patient improved. No surgical measures have as yet been considered.

MADERO, México, D. F., Mexico.

COLONIC INTUSSUSCEPTION: REPORT OF THREE CASES IN WHICH THE PATIENTS WERE TREATED WITH BARIUM SULFATE ENEMAS UNDER PRESSURE. JESÚS LOZOYA S. and FELIPE CACHO, Bol. méd. d. Hosp. inf., México **1**:17 (July-Aug.) 1944.

The authors describe 3 cases in which the diagnosis of colonic intussusception was made in the ward. In all 3 cases, barium sulfate enemas under pressure were applied under fluoroscopic control, with reduction of the intussusception in each instance.

The authors do not advise this kind of treatment for any other type of intussusception.

MADERO, México, D. F., Mexico.

MIKULICZ'S SYNDROME. DARÍO SEPULVEDA, Pediat. Américas **5**:129 (March) 1947.

This article is a review of the literature on Mikulicz' syndrome and the report of a case of a 5 year old girl who presented on her admission to the hospital swelling of the parotid and submaxillary glands. Her condition was diagnosed posteriorly as lymphatic leukemia. Postmortem study showed intense lymphocytic infiltration of the parotid and submaxillary glands.

DE LA TORRE, México, D. F., Mexico.

Diseases of the Muscles, Bones, Joints and Lymph Glands

BONE LESIONS ENCOUNTERED DURING INFANCY. ARTHUR E. CHILDE, Canad. M. A. J. **56**:292 (March) 1947.

A brief review of lesions of bone occurring during infancy is presented. The conditions described are rickets, infantile scurvy, celiac disease, congenital syphilis, infantile pyogenic osteomyelitis, tuberculosis, sarcoidosis, lead poisoning, osteopetrosis, cretinism, osteogenesis imperfecta, sympathetic neuroblastomas, leukemia, achondroplasia fetalis, eccentro-osteochondrodysplasia (Morquio's disease), lipochondrodystrophy (gargoylism), dyschondroplasia (hereditary deforming chondrodysplasia) and infantile cortical hyperostosis.

MOORE, Omaha.

TREATMENT OF OSTEOMYELITIS WITH INDUCTOTHERMY. NICANDRO CHÁVEZ, Bol. méd. d. Hosp. inf., México **1**:31 (July-Aug.) 1944.

In the first part of his article, the author explains inductothermy, the physical principles of short wave diathermy and its physiologic effect in osteomyelitis.

In the second part, and as an example of the beneficial effect of this sort of therapy, he reports on a patient thus treated. A boy, aged 12, was previously treated by other known methods, but instead of improving he became worse, to such a degree that the amputation of the affected limb was considered. Under these conditions, treatment with inductothermy was begun, with favorable results. In five months of treatment, the improvement has been striking.

MADERO, México, D. F., Mexico.

PREMATURE SYNOSTOSIS OF THE SKULL IN INFANTS. LORENZO EXPÓSITO, Rev. cubana pediat. **18**:497 (Aug.) 1946.

The author reports on 2 infants with premature synostosis of the skull. The first was an 8 month old girl who showed striking abnormalities clinically and an unusual malformation of the skull. The deformity in the other infant was not so evident on clinical examination but striking digitations appeared on the roentgenograms. There is a good discussion on previously reported cases and on the pathologic changes.

KEITH, Rochester, Minn.

CONGENITAL MYELOMUSCULAR DYSTROPHY, OR OPPENHEIM-WERDNIG-HOFFMAN DISEASE. SANTIAGO CAVENGT, Acta pediat. españ. **4**:759 (June) 1946.

The author states that the spinal muscular atrophies known as Oppenheim disease and (amyotonia congenita) Werdnig-Hoffman disease (a form of hereditary muscular atrophy), must be considered as one and the same disease. He considers the differences reported between the two as due to observation of different stages in the evolution of the same disease.

Clinical and pathologic observations showed that the disease has two phases in chronologic order. The first phase, the hypotonic-atrophic (Oppenheim) may evolve to (*a*) spontaneous cure, which is exceptional, (*b*) death due to respiratory complications, which is frequent, or (*c*) the second or atrophic-paralytic phase (Werdnig-Hoffman) of variable duration.

The author presents 9 cases, 1 with spontaneous cure and another with slow progressive improvement. There is an extensive discussion of the problem.

KEITH, Rochester, Minn.

Directory of Pediatric Societies *

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Place: Salt Lake City General Hospital. Time: First Thursday of each month. 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Howard W. Brayton, 179 Allyn Street, Hartford 3, Conn.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. Clarence L. Lyon, 407 Riverside Ave., Spokane 8, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. William D. Rothwell Jr., Republic Bldg., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of the Colorado General Hospital. Time: Monthly from October to June.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6, Ala.
Place: Montgomery, Ala. Time: September 1949

ARIZONA PEDIATRIC SOCIETY

President: Dr. Hugh Thompson Jr., 110 S. Scott St., Tucson, Ariz.
Secretary: Dr. James R. Sickler, Physicians Bldg., Tucson, Ariz.
Place: Phoenix or Tucson. Time: On call.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.
Place: Los Angeles. Time: April 1949.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Lee Bivings, 20 Fourth St. N. W., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. H. L. F. Locke, 179 Allyn St., Hartford, Conn.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown, Conn.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville, Ill.
Place: Palmer House, Chicago. Time: May 10-12, 1949.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bdg., Davenport.
Place: Des Moines. Time: April 1949.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.
Place: New Orleans. Time: May 7, 1949.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SECTION

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. George Clark, 1817 Vinton St., Omaha.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW JERSEY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Robert E. Jennings, 117 Washington St., East Orange.
Secretary: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.
Secretary: Dr. Charles H. Gay, 1523 Elizabeth Ave., Charlotte, N. C.

Northern California Pediatric Society

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

Philippine Pediatric Society

President: Dr. Alberto V. Tupas, Department of Pediatrics, College of Medicine, University of the Philippines, Manila, Philippines.
Secretary: Dr. Artemio P. Jongco, Department of Pediatrics, College of Medicine, University of the Philippines, Manila, Philippines.
Place: Philippine General Hospital. Time: Every two months.

South Carolina Pediatric Society

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

Tennessee Pediatric Society

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

Texas Pediatric Society

President: Dr. John K. Glen, 4412 Montrose St., Houston.
Secretary-Treasurer: Dr. James N. Walker, 3616 Tulsa Way, Fort Worth 7.
Place: San Antonio. Time: Oct. 7-8, 1949.

Virginia Pediatric Society

President: Dr. C. P. Brown, 142 W. York St., Norfolk.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

Wisconsin State Medical Society, Section on Pediatrics

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Baltimore City Medical Society, Pediatric Section

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore .
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

Bronx Pediatric Society

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. William A. Schonfeld, 211 W. 106th St., New York 25.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Walter R. Coles, 604–2d St., Brooklyn.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. John L. Reichert, 1791 Howard St., Chicago 26.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Tuesday of each month.

Detroit Pediatric Society

President: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2.
Secretary: Dr. S. S. Bernstein, 650 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

Fort Worth Pediatric Society

President: Dr. Frank Cohen, 712 S. Henderson, Fort Worth, Texas.
Secretary: Dr. H. H. Womack, 1422 Pennsylvania, Fort Worth, Texas.
Place: Welch and West Restaurant. Time: Third Friday of each month.

Honolulu Pediatric Society

President: Dr. Donald Marshall, Medical Group, Honolulu.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu

Houston Pediatric Society

President: Dr. Edward O. Fitch, 3720 Fannin St., Houston, Texas.
Secretary: Dr. Thomas J. Donovan, 3506 Sunset Blvd., Houston 5, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

KNOXVILLE-OAK RIDGE PEDIATRIC SOCIETY

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn 16.
Secretary: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn 13.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2032 Belmont Rd. N.W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N.W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. James Conway, 1721 E. Lake Bluff Blvd., Milwaukee 11, Wis.
Secretary-Treasurer: Dr. Walter Polacheck, 425 E. Wisconsin Ave., Milwaukee 2, Wis.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October and December.

NASHVILLE PEDIATRIC SOCIETY

President: Dr. John M. Lee, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Dan S. Sanders Jr., 2103 Hayes St., Nashville, Tenn.
Time: Third Thursday of every month.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Milton Rapoport, 741 S. 3d St., Philadelphia.
Secretary: Dr. D. Stewart Polk, W. Montgomery Ave., Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. J. A. Gilmartin, 3708–15th Ave., Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

PORTLAND (ORE.) ACADEMY OF PEDIATRICS

President: Dr. Walter Goss, 1130 S. W. Morrison St., Portland.
Secretary-Treasurer: Dr. S. Gorham Babson, Medical Arts Bldg., Portland 5.
Place: University Club. Time: 6:30 p. m., first Monday of each month from September to June, inclusive.

QUEENS PEDIATRIC SOCIETY

Chairman: Dr. Walter C. A. Steffen, 42-28 Union St., Flushing, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 33-03 Parsons Blvd., Flushing, N. Y.
Place: Forest Hills, N. Y. Time: Third Monday of October, February, April; first Monday of December.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Merl J. Carson, 500 S. Kingshighway, St. Louis.
Secretary-Treasurer: Dr. Jackson K. Eto, 734 Missouri Theatre Bldg., St. Louis 3.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

SAN ANTONIO PEDIATRIC SOCIETY

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Clement H. Maloney, Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.

WACO PEDIATRIC SOCIETY

President: Dr. M. C. Carlisle, 1410 Austin Ave., Waco, Texas.
Secretary: Dr. F. W. Hoehn, 1422 Austin Ave., Waco, Texas.
Place: Provident Hospital, 1725 Colcord, Waco, Texas. Time: Third Thursday of each month.

WESTCHESTER COUNTY MEDICAL SOCIETY, PEDIATRICS SECTION (NEW YORK)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).